Not for publication or presentation

A G E N D A
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Orlando, FL
Saturday, February 22, 2020 2:45 – 4:45 PM

Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute; Telephone: 813-745-2556; E-mail: joseph.pidala@moffitt.org**
Co-Chair:	**Madan Jagasia, MD, MS, MMHC, Vanderbilt University Medical Center, Nashville, TN; Telephone: 615-936-8422; E-mail: madan.jagasia@vumc.org**
Co-Chair:	**Margaret MacMillan, MD, MSc; University of Minnesota, Minneapolis, MN; Telephone: 612-626-2961, E-mail: macmi002@umn.edu**
Scientific Director:	**Mukta Arora, MD, MBBS, MS, University of Minnesota Medical Center, Minneapolis, MN; Telephone: 612-626-4105; E-mail: arora005@umn.edu**
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Statistician:	**Karen Chen, MS, CIBMTR Statistical Center, Milwaukee, WI; Telephone: 414-805-0834; E-mail: kachen@mcw.edu**

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1. **Introduction**
   a. Minutes and Overview Plan from February 2019 meeting (Attachment 1)
   b. Introduction of new incoming Co-Chair:
      Carrie Kitko, MD
      Vanderbilt University Medical Center
      Telephone: (615) 936-2088
      E-mail: carrie.l.kitko@vumc.org

      Thank you to **Joseph Pidala** for all of his contributions and input to the GVWC.

2. **Accrual Summary** (Attachment 2)

3. **Presentations, published or submitted papers**
   a. **GV14-01b** Hamilton BK, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Chhabra S, et. al. Comparative analysis of calcineurin inhibitor-based methotrexate and mycophenolate mofetil-containing regimens for prevention of graft-versus-host disease after reduced-intensity conditioning allogeneic transplantation. ***Biology Blood Marrow Transplant.*** **2019 Jan 25.**
   b. **GV16-01b** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for pediatric patients with acute leukemia. ***Blood Advances.*** **2019 May 14.**

c. **GV16-02** Saad A, Wang T, Hemmer MT, Spellman SR, Arora M, Lamb LS, Hashmi SK. Impact of T-cell dose on graft-versus-host disease risk after allogeneic HLA-matched peripheral blood stem cell transplantation. ***Biology Blood Marrow Transplant.*** **2019 Sep.**
d. **GV17-02** Im A, Wang T, Hemmer MT, Spellman SR, Arora M, Majhail NS, Pavletic SZ, Weisdorf DJ, Rashidi A, Hamilton BK. Risk factors of acute and chronic GVHD in haploidentical hematopoietic cell transplantation using post-transplant Cyclophosphamide. ***Submitted.***
e. **GV17-01** Elgarten C, Li Y, Huang Y-S, Hall M, Aplenc R, Hemmer MT, Arora M, Spellman SR, Wang T, Fisher BT. Early broad-spectrum antibiotics and risk of acute graft-versus-host disease in children: an analysis from the CIBMTR and the Pediatric Health Information System (PHIS). ***ASH oral presentation. December 2019.***
f. **GV17-03** Saliba RM, Arora M, Spellman SR, Hemmer MT, Wang T, Alousi A, Pidala JA, Jagasia M, MacMillan ML, Horowitz MM, Schriber J, Champlin RE, Ciurea S. Acute Graft-Versus-Host Disease Is Less Severe and Associated with Lower Non-Relapse Mortality after Haploidentical Transplantation with Post-Cyclophosphamide Prophylaxis. ***TCT oral presentation. February 2020.***

4. Studies in progress (Attachment 3)

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc) **Manuscript Preparation**
b. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber) **Manuscript Preparation**
c. **GV18-01** Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR) **Protocol Development**
d. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A) **Protocol Development**
e. **GV18-03** Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ) **Protocol Development**
f. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A) **Sample Typing**

5. Future/proposed studies

a. **PROP 1911-80/1911-175** Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies (N Sharma/L Metheny/M Byrne/M de Lima/Y Efebera) (Attachment 4)
b. **PROP 1911-52** HLA-DQ2/DQ8 and GVHD risk in pediatric patients undergoing hematopoietic stem cell transplant (A Seif) (Attachment 5)
c. **PROP 1911-81** Investigate the association of HLA-A*0101 allele expression and risk for acute cutaneous GVHD (A Markova/A Jakubowski/D Ponce) (Attachment 6)
d. **PROP 1911-252** Prediction of graft-versus-host disease in recipients of hematopoietic cell transplant from a single mismatched unrelated donor using a highly-multiplexed proteomics assay: MHC-PepSeq (K Sandhu/J Altin/M Askar/R Nakamura) (Attachment 7)
e. **PROP 1911-102** Machine learning models and clinical decision support tool for acute and chronic graft versus host disease (GvHD) in patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplant (HCT) (T Kindwall-Keller/B Lobo) (Attachment 8)
f. **PROP 1911-270** Clinical significance of pediatric late acute GVHD and chronic GVHD: why does it matter to differentiate? (T Takahashi/M MacMillan) (Attachment 9)

g. **PROP 1911-25** Influence of combination of GVHD prophylaxis and stem cell source on GRFS (S Farhan) (Attachment 10)
h. **PROP 1912-01** Exploring the impact of allogeneic stem cell transplant volume on GRFS: a matched cohort study in contemporary era (R Shallis/L Gowda/A Zeidan/B Betts) (Attachment 11)
i. **PROP 1906-03/1911-31/1911-139/1911-169/1911-196** Comparison of outcomes with post-transplant cyclophosphamide (pCY) in haploidentical donor transplant (HIDT) versus 8/8 HLA-matched related and unrelated, and 7/8 mismatched unrelated donor allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome (D Modi/F Socola/K Caldwell) (Attachment 12)

Dropped proposed studies

j. **PROP 1909-07** Matched control dataset from CIBMTR for an FDA requested phase II expansion cohort study on CD24Fc in prophylaxis of acute GVHD in myeloablative matched unrelated donor HCT. *Forwarded to CIBMTR Corporate Program.*
k. **PROP 1911-21** Use of therapeutic agents for treatment of steroid-refractory GVHD before and after FDA approval of ruxolitinib and ibrutinib. *Data for steroid refractory GVHD is unavailable.*
l. **PROP 1911-152** Is age an independent risk factor in younger age allogeneic stem cell transplant recipients with hematological malignancies (age 0.1-29.99 years) for grade II-IV acute GVHD and chronic GVHD? *Overlap with CIBMTR study GV14-02.*
m. **PROP 1911-154** Validating predictive biomarkers of aGVHD from a humanized mouse model of HSCT. *Post-transplant samples not available in CIBMTR sample repository.*
n. **PROP 1911-183** Graft-versus-host-disease (GVHD) relapse-free survival (GRFS) and chronic GVHD relapse free survival (CRFS) following haploidentical transplant for hematological malignancies: a comparison of T cell replete vs ex vivo T cell depletion approaches in a contemporary cohort of patients. *Sample size issue.*
o. **PROP 1911-212** Can calcineurin inhibitors be avoided for GVHD prophylaxis for umbilical cord transplant recipients in the era of anti-thymocyte globulin (ATG)? *Sample size issue.*
p. **PROP 1911-219** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myeloid neoplasms. *Sample size issue.*
q. **PROP 1911-233** Mesenchymal stem cells (MSC) as therapy for steroid refractory acute graft versus host disease (SRaGVHD) in patients undergoing allogenic stem cell transplant. *Data for steroid refractory GVHD and response to GVHD therapy is unavailable.*
r. **PROP 1911-240** Impact of cryopreservation versus fresh donor lymphocyte infusions on non-relapse and relapse mortality/morbidity. *Data on cryopreservation status is unavailable.*
s. **PROP 1911-241** Comparison of graft versus host disease (GVHD) and survival outcomes in alternate mismatched graft sources for allogeneic transplant. *Sample size issue.*

6. Other Business

MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR GRAFT-VERSUS-HOST DISEASE
Houston, TX
Wednesday, February 20, 2019 12:15 – 2:15 PM

Co-Chair:	**Amin Alousi, MD, MD Anderson Cancer Center, Houston, TX;**
	Telephone: 713-745-8613; E-mail: aalousi@mdanderson.org
Co-Chair:	**Joseph Pidala, MD, PhD, H. Lee Moffitt Cancer Center and Research Institute;**
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Co-Chair:	**Madan Jagasia, MBBS, MS, Vanderbilt University Medical Center, Nashville, TN;**
	Telephone: 615-936-8422; E-mail: madan.jagasia@vumc.org
Scientific Director:	**Mukta Arora, MD, MS, University of Minnesota Medical Center, Minneapolis, MN;**
	Telephone: 612-626-4105; E-mail: arora005@umn.edu
Scientific Director:	**Stephen Spellman, MBS, CIBMTR Statistical Center, Minneapolis, MN;**
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1. Introduction

The CIBMTR Graft-versus-Host Disease Working Committee (GVWC) was called to order at 12:15 pm by Dr. Amin Alousi. The GVWC Leadership was introduced to the GVWC members. Dr. Alousi introduced the new incoming GVWC Co-Chair, Dr. Margaret (Margy) MacMillan, who would be replacing Dr. Alousi, who had fulfilled his 5-year term as Co-Chair. Dr. Alousi reminded those in attendance that scanning their badges as they entered the conference room would include them in the GVWC email list, so they would receive invitations to participate in new studies seeking input. The voting sheet was explained and presenters were reminded they would be allowed 5 minutes to present, followed by approximately 5-10 minutes for discussion. Dr. Joseph Pidala thanked Dr. Alousi for his contributions to the GVWC and presented him with a gift.

2. Accrual Summary (Attachment 2)

Dr. Mukta Arora presented an overview of the CIBMTR, BMT CTN and Chronic GVHD Consortium research repository collections, and encouraged prospective investigators to utilize this resource to further enhance their proposals or studies.

3. Presentations, published or submitted papers

Dr. Arora referenced the publications and submissions, noting that there was an omission in this section. Study **GV15-02**, led by Amin Alousi, which evaluated the composite endpoint of GVHD-free, relapse-free survival between matched unrelated donors with bone marrow versus peripheral blood stem cells.

a. **GV14-01a** Chhabra S, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Hamilton BK, et. al. ***Biology Blood Marrow Transplant.* 2018 Aug 25.**

b. **GV14-01b** Hamilton BK, Liu Y, Hemmer MT, Costa L, Pidala JP, Couriel DR, Alousi AM, Majhail NS, Stuart RK, Kim D, Ringden O, Spellman SR, Arora M, Chhabra S, et. al. ***Submitted.***

c. **GV15-01b** Turcotte L, Wang T, Hemmer MT, Spellman SR, Arora M, Yingst A, Couriel DR, Alousi AM, Pidala J, Knight JM, Verneris MR. Proinflammatory cytokine and adipokine levels in adult unrelated marrow donors are not associated with hematopoietic cell transplantation outcomes. ***Biology Blood Marrow Transplant.* 2018 Aug 23.**

d. **GV16-01a** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for adult patients with acute leukemia. ***Submitted.***

e. **GV16-01b** Mehta R, Holtan S, Wang T, Hemmer MT, Arora M, Spellman SR, Alousi AM, Couriel DR, Pidala J, Weisdorf D. GVHD-free, relapse-free survival (GRFS) and chronic GVHD-free, relapse-free survival (CRFS) in alternative donor hematopoietic cell transplantation for pediatric patients with acute leukemia. ***Submitted.***

f. **GV16-02** Saad A, Wang T, Hemmer MT, Spellman SR, Arora M, Lamb LS, Hashmi SK. Impact of T-cell dose on graft-versus-host disease risk after allogeneic HLA-matched peripheral blood stem cell transplantation. ***Poster presentation at ASH meeting in San Diego, CA, December 2018.***

g. **GV17-02** Im A, Wang T, Hemmer MT, Spellman SR, Arora M, Majhail NS, Pavletic SZ, Weisdorf DJ, Rashidi A, Hamilton BK. Risk factors of acute and chronic GVHD in haploidentical hematopoietic cell transplantation using post-transplant Cyclophosphamide. ***Poster presentation at TCT meeting in Houston, TX, February 2019.***

4. Future/proposed studies

a. **PROP 1803-03** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gills/ E Padron/ A Lazaryan) (Attachment 3)

Dr. Nancy Gillis presented the proposal. The stated hypothesis is that donor-engrafted clonal hematopoiesis (CH) is associated with an increased risk of GVHD among adult allogeneic HCT recipients. The specific aims of the proposed study are to determine the prevalence of CH in matched sibling and unrelated allogeneic HCT, determine if allogeneic HCT from donors with CH is associated with an increased risk of acute and chronic GVHD, and whether CH mutations are present in donor-engrafted T-cells. This proposal could change pre-HCT donor screening, as well as disentangle the effect of donor age versus CH status on GVHD risk.

A member of the GVWC Leadership asked whether CHIP mutations have been analyzed in a post-transplant setting before, to which Dr. Gillis responded that they have not but feel they plan to use the same strategy used in their pre-transplant sequencing. A GVWC member asked if the proponents have secured funding for this study, as there seems to be a lot of sample analysis that will be required. The proponents have not secured funding, as of yet. Another member of the GVWC raised the issue that it may not be possible to make a conclusion of CHIP on GVHD, since CHIP mutations are typically myeloid while GVHD occurs from lymphoid T-cells. Dr. Gills mentioned

that there is some data of fewer CHIP in lymphoid cells. Regarding assessment of CHIP in donor engrafted T-cells, another member commented that since mostly allo-reactive T cells cause acute GVHD whereas auto-reactive T cells could cause CGVHD, this phenomenon may result in positive results for CGVHD but not acute GVHD. Dr. Gillis mentioned that the recent European publication, which documented an association between CHIP and chronic GVHD, illustrated that there are associations to be made. However, as another GVWC member stated, this phenomenon could be connected between CHIP and chronic GVHD but will likely prove impossible to analyze acute GVHD. It was confirmed that donors with these samples available have consented for research. These samples are coming from the NMDP Biorepository, whose donors and recipients have all consented for research.

b. **PROP 1810-08/1811-55** Determining the optimal ATG dosing in conditioning regimen in patients with hematologic malignancies (M Byrne/ L Metheny/ M de Lima) (Attachment 4)
Dr. Michael Byrne presented the proposal. The hypothesis of the proposal is that ATG dose and pre-HCT absolute lymphocyte count (ALC) will influence post-HCT outcomes, specifically incidence and severity of GVHD, NRM and OS. The scientific impact of this study is that such a large-scale analysis to identify an optimal dose of ATG has not been undertaken. The results of the analysis on these outcomes may inform future ATG dosing, and if the hypothesis is disproven, transplant providers will be encouraged to continue to dose ATG in their existing fashion.
A member of the GVWC stated that they worked on a study that evaluated the half life of rabbit ATG and that the timing of ATG administration made a difference in outcomes. At the meeting, the GVWC Leadership said that date of ATG administration was not captured, but in this population in the proposal, date of ATG administration would be collected. Another clarification from the GVWC was that source of ATG is collected by the CIBMTR. ATG source is collected, although the population described in the proposal has already been restricted to rabbit ATG. Another comment from the GVWC was to consider restricting the population to one disease type, specifically aplastic anemia was suggested, in an effort to make the study more homogenous with respect to disease.

c. **PROP 1811-34** Cyclosporine vs tacrolimus based GVHD prophylaxis in children undergoing allogeneic hematopoietic cell transplantation (L Broglie/ P Satwani/ L Davis) (Attachment 5)
Dr. Laurie Davis presented the proposal. The proposal's hypothesis is that cyclosporine-based GVHD prophylaxis in children is associated with a lower incidence of cGVHD compared to tacrolimus-based regimens. If this hypothesis is not disproven, it will encourage a change in practice in terms of GVHD prophylaxis treatment for pediatric patients, which would result in lower rates of cGVHD and long-term morbidity.
A member of the GVWC asked if the CIBMTR collects dose information on methotrexate used in GVHD prophylaxis, which unfortunately the CIBMTR forms do not collect. Another member of the GVWC asked if the proponents would evaluate MMF versus methotrexate, in addition to the stated goal of comparing cyclosporine versus tacrolimus.

d. **PROP 1811-163** Racial and ethnic differences in patients with chronic graft versus host disease (N Farhadfar/ J Wingard/ S Lee) (Attachment 6)
Dr. Nosha Farhadfar presented the proposal. Dr. Farhadfar stipulated that racial background on clinical outcomes of patients who develop post-HCT cGVHD has been addressed in several studies, but the true impact has not yet been adequately evaluated in a large-scale analysis. The proposal hypothesizes that there are racial differences in clinical manifestations, severity, treatment patterns and outcome of patients with cGVHD, and Dr. Farhadfar stated that this would be the first study to make such an investigation. If these characteristics do differ between racial groups, it may be possible to identify groups of patients with poor outcomes who should be considered for analysis in future clinical trials. This proposed study would also evaluate whether there is appropriate representation of minorities in clinical trials.

A member of the GVWC Leadership clarified that the CIBMTR did not collect NIH Global Severity of cGVHD to be able to be analyzed in this population proposed, but data are available on organ involvement, severity (mild, moderate, severe) and extent (limited, extensive) of cGVHD. A GVWC member asked if this proposal would restrict the population to 1 country, which it currently is not, and recommended restricting to 1 country to remove the heterogeneous factors of including multiple countries. Another GVWC member asked if donor race and ethnicity would be evaluated, and Dr. Farhadfar noted that none of the referenced publications evaluated donor race. Another GVWC member noted that there were no patients of the Hispanic race described in the population, and Dr. Farhadfar clarified that the patients' ethnicity is described in the proposal table. The next GVWC member noted that Hispanic ethnicity is not a race, and should not be treated as a category to compare against Caucasians, African-Americans and Asian/Pacific Islanders. This GVWC member also noted that some centers may have done single center studies examining this question, and perhaps this question could be better suited by a single (or several) center study. Another GVWC member noted that there is a big discrepancy in donor type between the different patient racial groups, and may prove difficult to analyze.

Dropped proposed studies

Dr. Arora explained that there were some proposals that were not presented at this meeting, due to factors related to data availability. Due to that, Dr. Arora briefly explained the difference between the CIBMTR's two tracks of data collection, Transplant Essential Data (TED) which collects more broad data on a wider population and Comprehensive Report Forms (CRF) which collects more detailed information on a subset of the patients completing TED forms. The main point relevant to the GVWC is that necessary post-HCT GVHD data has only been collected on the CRF forms. As of 2017, the TED follow-up forms began collecting more detailed GVHD data so it is possible to use TED patients to analyze GVHD in the detailed standard that GVWC studies require. Also, since 2017, data have been collected to calculate NIH Global Severity of cGVHD, so that is an outcome that can hopefully be evaluated soon in retrospective studies.

e. **PROP 1811-158** Role of post-allogeneic hematopoietic cell transplant hypomethylating agents on the incidence and severity of graft-versus-host disease in patients with myelodysplastic syndrome and acute myeloid leukemia. *Small sample size of patients with valid date available for post-HCT hypomethylating agents. Also, it was pointed out that dates of initiating hypomethylating agent were not collected, hence its trajectory with regards to GVHD (whether it was administered prior to development of acute GVHD or not) is unknown.*
f. **PROP 1812-08** The impact of recipient abnormal Stimulator of Interferon Genes (STING) genotypes on acute and chronic graft-versus-host disease after matched unrelated donor allogeneic HCT. *Withdrawn by proponents based on data provided to them evaluating a pre-existing dataset.*

5. Studies in progress (Attachment 7)

Dr. Arora presented a slide that illustrated the current status of the active studies.

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc) **Protocol Development**
b. **GV17-03** Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber) **Analysis**
c. **GV18-01** Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR) **Protocol Development**

b. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A) **Data File Preparation**
b. **GV18-03** Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ) **Protocol Development**

6. Other Business

Dr. Arora reminded the GVWC members that the leadership would remain at the table for 10-15 minutes after the meeting if anyone had questions or comments. Hearing no other calls for business, Dr. Arora adjourned the meeting at 1:45 PM.

After the new proposals were presented, each participant in the meeting had the opportunity to rate each proposal using paper ballots. Based on the voting results, current scientific merit, available number or relevant cases and the impact of the study on the field, the following study will move forward as a part the committee's research portfolio for the upcoming year:

PROP 1803-03 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gills/ E Padron/ A Lazaryan)

Working Committee Overview Plan for 2019 – 2020

a. **GV17-01** Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten / B Fisher / R Aplenc)

The aims of the study are to determine the association of antibiotics commonly administered for neutropenic fever with subsequent development of post-HCT aGVHD among pediatric patients undergoing HCT for acute leukemia. The hypothesis is that these patients who are exposed to antibiotics with activity against anaerobic commensal microorganisms are associated with an increased risk of aGVHD.

We anticipate the results will be finalized and an abstract for ASH submitted by August 2019. The initial manuscript is expected to be received by September 2019 and will be revised and circulated to the Writing Committee by November 2019. We finally expect to submit the final manuscript for publication by January 2020. 80 statistical hours have been allocated to accomplish these goals (PHIS statisticians will perform the multivariate analysis).

b. **GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT (R Saliba / S Ciurea / J Schriber)

The aims of the study are to compare aGVHD, cGVHD, OS and TRM between patients receiving post-transplant Cyclophosphamide-based GVHD prophylaxis with those receiving standard GVHD prophylaxis. Patients over the age of 60, and therefore at greater risk for GVHD, will also be specifically examined in a subset analysis.

We anticipate that an ASH abstract will be submitted by August 2019. Further, the initial draft of the manuscript is expected to be received by August 2019 and circulated to the Writing Committee by September 2019. The final manuscript will be submitted by November 2019. 70 statistical hours have been allocated to accomplish these goals.

c. **GV18-01** Comparison of late effects among alloHCT survivors with and without cGVHD (C Lee/ D Couriel)
This study will test whether the cumulative incidence rate of late effects is greater among alloHCT survivors with cGVHD versus those without cGVHD.
We anticipate circulating the revised protocol to the GVWC by October 2019, and then finalizing the protocol by December 2019. We further anticipate preparing the data file for analysis by March 2020. 200 statistical hours have been allocated to accomplish these goals.

d. **GV18-02** Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD (W Wallis/ A Alousi/ A Gulbis)
This study will evaluate the cumulative incidence of bacterial blood stream infections in patients with aGVHD grade II-IV, and compare patients between centers that give antibiotics for antibacterial prophylaxis versus those centers that do not.
We anticipate having the data file prepared for analysis by July 2019, with the aspirations to submit an abstract to ASH by August 2019. We further anticipate receiving the initial draft of the manuscript by October 2019, and circulating a revised draft to the Writing Committee by December 2019. We finally expect to submit the final manuscript for publication by March 2020. 130 statistical hours have been allocated to accomplish these goals.

e. **GV18-03** Impact of chronic GVHD on non-relapse mortality and disease relapse (V Bhatt/S Lee)
This study will evaluate the cumulative incidence of non-relapse mortality and relapse between patients who have cGVHD versus those without cGVHD, as well as between older versus younger patients.
We anticipate circulating the revised protocol to the GVWC by November 2019, and then finalizing the protocol by January 2020. 100 statistical hours have been allocated to accomplish this goal.

f. **GV19-01** Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (N Gillis/ E Padron/ A Lazaryan)
This study will investigate the incidence of clonal hematopoiesis among matched sibling and unrelated donors, as well as determine if clonal hematopoiesis is associated with an increased rate of acute and chronic GVHD.
We anticipate receiving the draft protocol by July 2019, and finalizing the protocol by October 2019. 100 statistical hours have been allocated to accomplish this goal.

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2019	Hours allocated 7/1/2018-6/30/2019	Total Hours allocated
GV17-01 Investigating antibiotic exposure and risk of aGVHD in children undergoing HCT for acute leukemia	Protocol development	Submission – Jan 2020	250	**250**	170	80	**250**
GV17-03 Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT	Data file preparation	Submission – Nov 2019	155	**155**	85	70	**155**
GV18-01 Comparison of late effects among alloHCT survivors with and without cGVHD	Protocol pending	Analysis – Mar 2020	310	**200**	0	200	**200**
GV18-02 Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD	Protocol development	Submission – Mar 2020	300	**300**	170	130	**300**
GV18-03 Impact of chronic GVHD on non-relapse mortality and disease relapse	Protocol pending	Data file prep – Jan 2020	310	**100**	0	100	**100**
GV19-01 Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients	Protocol pending	Data file prep – Nov 2019	310	**100**	0	100	**100**

Oversight Assignment for Working Committee Leadership (March 2019)

Joseph Pidala	**GV17-03** Characteristics and outcomes of acute and chronic GVHD after haploidentical related donor allogeneic HCT **GV18-01**: Comparison of late effects among alloHCT survivors with and without cGVHD
Madan Jagasia	**GV18-02**: Comparison of antibacterial prophylaxis strategies and outcomes in alloHCT patients with acute GVHD **GV18-03**: Impact of chronic GVHD on non-relapse mortality and disease relapse
Margy MacMillan	**GV17-01**: Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia **GV19-01**: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients

Accrual Summary for the Graft-vs-Host Disease Working Committee

Characteristics of leukemia patients receiving allogeneic HCT between 1990-2019

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**29438**	**4422**	**1824**	**35528**	**7162**
Number of centers	450	317	305	405	253
Age at transplant, years, median (range)	39 (<1-78)	43 (<1-88)	35 (1-79)	43 (<1-83)	20 (<1-83)
Disease					
AML	11281 (38)	1934 (44)	792 (43)	13481 (38)	3302 (46)
ALL	5560 (19)	973 (22)	431 (24)	6601 (19)	2328 (33)
Other leukemia	1415 (5)	164 (4)	91 (5)	1768 (5)	296 (4)
MDS	4548 (15)	955 (22)	297 (16)	7801 (22)	941 (13)
CML	6634 (23)	396 (9)	213 (12)	5877 (17)	295 (4)
Sex					
Male	17215 (58)	2663 (60)	1076 (59)	20845 (59)	3974 (55)
Female	12220 (42)	1759 (40)	748 (41)	14680 (41)	3188 (45)
Missing	3 (<1)	0	0	3 (<1)	0
Graft source					
BM	15053 (51)	1820 (41)	579 (32)	17129 (48)	-
PBSC	13538 (46)	2564 (58)	1136 (62)	17960 (51)	-
Missing	847 (3)	38 (1)	109 (6)	439 (1)	-
GVHD prophylaxis					
Ex-vivo T-cell depletion	1624 (6)	584 (13)	183 (10)	2940 (8)	49 (1)
CD34 selection	442 (2)	201 (5)	115 (6)	633 (2)	257 (4)
Post-tx Cyclophosphamide +/- others	272 (1)	2299 (52)	165 (9)	719 (2)	9 (<1)
Tac + MTX	3387 (12)	110 (2)	158 (9)	8210 (23)	214 (3)
Tac + MTX + others	759 (3)	25 (1)	35 (2)	3333 (9)	81 (1)
Tac + MMF	593 (2)	206 (5)	39 (2)	1651 (5)	1093 (15)
Tac + MMF + others	168 (1)	43 (1)	14 (1)	757 (2)	295 (4)
Tac	404 (1)	36 (1)	28 (2)	925 (3)	197 (3)
Tac + others	441 (1)	18 (<1)	19 (1)	970 (3)	254 (4)
CsA + MTX	13234 (45)	523 (12)	255 (14)	8530 (24)	251 (4)
CsA + MTX + others	597 (2)	36 (1)	28 (2)	1826 (5)	91 (1)
CsA + MMF	826 (3)	30 (1)	37 (2)	1285 (4)	2111 (29)
CsA + MMF + others	42 (<1)	3 (<1)	3 (<1)	352 (1)	375 (5)
CsA	3300 (11)	100 (2)	95 (5)	868 (2)	1169 (16)
CsA + others	284 (1)	23 (1)	10 (1)	337 (1)	256 (4)
Others	555 (2)	31 (1)	44 (2)	354 (1)	121 (2)
Missing	2510 (9)	154 (3)	596 (33)	1838 (5)	339 (5)

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Conditioning regimen intensity					
Myeloablative	23382 (79)	2510 (57)	1101 (60)	24491 (69)	5019 (70)
Reduced intensity	2723 (9)	543 (12)	227 (12)	7003 (20)	753 (11)
Non-myeloablative	926 (3)	1169 (26)	134 (7)	1866 (5)	1044 (15)
Missing	2407 (8)	200 (5)	362 (20)	2168 (6)	346 (5)
Acute GVHD grade					
None	13439 (46)	1886 (43)	962 (53)	11590 (33)	2866 (40)
Grade I	4735 (16)	727 (16)	215 (12)	5758 (16)	1058 (15)
Grade II	4036 (14)	879 (20)	168 (9)	7703 (22)	1468 (20)
Grade III	3602 (12)	444 (10)	171 (9)	5288 (15)	877 (12)
Grade IV	1307 (4)	206 (5)	52 (3)	2823 (8)	393 (5)
Missing	2319 (8)	280 (6)	256 (14)	2366 (7)	500 (7)
Organ involvement of aGVHD					
Skin	1001 (11)	323 (21)	66 (17)	2772 (17)	522 (19)
Skin + Liver	1377 (15)	109 (7)	31 (8)	1595 (10)	113 (4)
Skin + Liver + LGI	1894 (21)	175 (11)	69 (18)	2646 (17)	244 (9)
Skin + Liver + UGI + LGI	345 (4)	52 (3)	19 (5)	849 (5)	126 (5)
Skin + LGI	1650 (18)	275 (18)	73 (19)	3047 (19)	527 (19)
Liver	295 (3)	24 (2)	14 (4)	259 (2)	44 (2)
Liver + LGI	320 (4)	33 (2)	4 (1)	334 (2)	61 (2)
Liver + UGI + LGI	135 (1)	24 (2)	4 (1)	198 (1)	57 (2)
LGI	715 (8)	126 (8)	39 (10)	1173 (7)	242 (9)
UGI + LGI	599 (7)	199 (13)	33 (8)	1212 (8)	369 (14)
Missing	675 (7)	190 (12)	39 (10)	1756 (11)	428 (16)
Incidence of cGVHD					
No	18671 (63)	3195 (72)	1391 (76)	20064 (56)	5270 (74)
Yes	9628 (33)	1119 (25)	323 (18)	13759 (39)	1640 (23)
Missing	1139 (4)	108 (2)	110 (6)	1705 (5)	252 (4)
Maximum grade of cGVHD					
Limited	3010 (31)	318 (28)	97 (30)	2800 (20)	623 (38)
Extensive	6430 (67)	784 (70)	215 (67)	10695 (78)	979 (60)
Missing	188 (2)	17 (2)	11 (3)	264 (2)	38 (2)
Overall severity of cGVHD					
Mild	3959 (41)	515 (46)	120 (37)	4651 (34)	933 (57)
Moderate	3386 (35)	365 (33)	111 (34)	4084 (30)	404 (25)
Severe	2019 (21)	212 (19)	76 (24)	2821 (21)	241 (15)
Missing	264 (3)	27 (2)	16 (5)	2203 (16)	62 (4)
Year of transplant					
1990-1994	8201 (28)	444 (10)	206 (11)	3096 (9)	33 (<1)

Accrual Table 1. Leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
1995-1999	7079 (24)	501 (11)	309 (17)	6186 (17)	407 (6)
2000-2004	5368 (18)	228 (5)	374 (21)	7810 (22)	922 (13)
2005-2009	4196 (14)	233 (5)	354 (19)	8726 (25)	2167 (30)
2010-2014	2327 (8)	633 (14)	221 (12)	4666 (13)	2266 (32)
2015-2019	2267 (8)	2383 (54)	360 (20)	5044 (14)	1367 (19)
Follow-up of survivors, months, median (range)	97 (<1-344)	33 (<1-335)	61 (1-334)	97 (<1-350)	71 (<1-284)

Abbreviations: AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, CML=Chronic myelogenous leukemia, MDS=Myelodysplastic-myeloproliferative diseases, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Characteristics of <u>non-leukemia</u> patients receiving allogeneic HCT between 1990-2019

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Number of patients	**13462**	**1803**	**1440**	**9538**	**3432**
Number of centers	442	246	288	328	216
Age at transplant, years, median (range)	26 (<1-79)	14 (<1-76)	20 (<1-77)	27 (<1-79)	5 (<1-73)
Disease					
NHL	3269 (24)	352 (20)	314 (22)	3052 (32)	556 (16)
HD	466 (3)	131 (7)	70 (5)	752 (8)	145 (4)
SAA	3429 (25)	292 (16)	207 (14)	1614 (17)	193 (6)
MM-PCD	1697 (13)	62 (3)	201 (14)	736 (8)	50 (1)
Inherited abnormalities of erythrocyte diff-or function	2986 (22)	324 (18)	207 (14)	976 (10)	567 (17)
SCID & other immune system disorders	649 (5)	437 (24)	303 (21)	998 (10)	774 (23)
Inherited abnormality of platelets	27 (<1)	3 (<1)	4 (<1)	41 (<1)	42 (1)
Histiocytic disorders	122 (1)	65 (4)	27 (2)	378 (4)	241 (7)
Inherited disorders of metabolism	211 (2)	90 (5)	28 (2)	547 (6)	754 (22)
Others	606 (5)	47 (3)	79 (5)	444 (5)	110 (3)
Sex					
Male	8021 (60)	1117 (62)	827 (57)	5949 (62)	2082 (61)
Female	5441 (40)	686 (38)	613 (43)	3589 (38)	1350 (39)
GVHD prophylaxis					
Ex-vivo T-cell depletion	592 (4)	361 (20)	146 (10)	896 (9)	15 (<1)
CD34 selection	255 (2)	153 (8)	96 (7)	389 (4)	58 (2)
Post-tx Cyclophosphamide +/- others	356 (3)	666 (37)	60 (4)	152 (2)	3 (<1)
Tac + MTX	974 (7)	22 (1)	40 (3)	1628 (17)	101 (3)
Tac + MTX + others	253 (2)	13 (1)	15 (1)	756 (8)	23 (1)
Tac + MMF	293 (2)	92 (5)	19 (1)	518 (5)	377 (11)
Tac + MMF + others	81 (1)	25 (1)	9 (1)	195 (2)	124 (4)
Tac	170 (1)	17 (1)	18 (1)	327 (3)	116 (3)
Tac + others	131 (1)	6 (<1)	3 (<1)	203 (2)	120 (3)
CsA + MTX	5580 (41)	181 (10)	202 (14)	1829 (19)	157 (5)
CsA + MTX + others	322 (2)	22 (1)	19 (1)	358 (4)	35 (1)
CsA + MMF	694 (5)	41 (2)	38 (3)	693 (7)	885 (26)
CsA + MMF + others	29 (<1)	1 (<1)	3 (<1)	116 (1)	119 (3)
CsA	1996 (15)	85 (5)	126 (9)	532 (6)	840 (24)
CsA + others	312 (2)	11 (1)	16 (1)	192 (2)	146 (4)
Others	210 (2)	24 (1)	25 (2)	123 (1)	47 (1)

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Missing	1214 (9)	83 (5)	605 (42)	631 (7)	266 (8)
Graft source					
BM	8162 (61)	958 (53)	625 (43)	5213 (55)	-
PBSC	4990 (37)	836 (46)	759 (53)	4168 (44)	-
Missing	310 (2)	9 (<1)	56 (4)	157 (2)	-
Conditioning regimen intensity					
Myeloablative	7909 (59)	777 (43)	736 (51)	3941 (41)	2097 (61)
Reduced intensity	1354 (10)	257 (14)	189 (13)	2520 (26)	523 (15)
Non-myeloablative	2580 (19)	564 (31)	199 (14)	2146 (22)	604 (18)
Missing	1619 (12)	205 (11)	316 (22)	931 (10)	208 (6)
Acute GVHD grade					
None	7721 (57)	942 (52)	950 (66)	4102 (43)	1674 (49)
Grade I	1745 (13)	237 (13)	119 (8)	1333 (14)	500 (15)
Grade II	1449 (11)	264 (15)	117 (8)	1582 (17)	558 (16)
Grade III	1236 (9)	155 (9)	83 (6)	1163 (12)	309 (9)
Grade IV	447 (3)	82 (5)	23 (2)	649 (7)	153 (4)
Missing	864 (6)	123 (7)	148 (10)	709 (7)	238 (7)
Organ involvement of aGVHD					
Skin	483 (15)	120 (24)	48 (22)	672 (20)	263 (26)
Skin + Liver	435 (14)	31 (6)	21 (10)	265 (8)	45 (4)
Skin + Liver + LGI	566 (18)	68 (14)	22 (10)	501 (15)	85 (8)
Skin + Liver + UGI + LGI	97 (3)	10 (2)	7 (3)	147 (4)	40 (4)
Skin + LGI	691 (22)	87 (17)	52 (24)	725 (21)	221 (22)
Liver	101 (3)	9 (2)	9 (4)	57 (2)	10 (1)
Liver + LGI	113 (4)	16 (3)	7 (3)	107 (3)	30 (3)
Liver + UGI + LGI	26 (1)	10 (2)	3 (1)	47 (1)	12 (1)
LGI	289 (9)	48 (10)	22 (10)	337 (10)	90 (9)
UGI + LGI	154 (5)	56 (11)	19 (9)	204 (6)	85 (8)
Missing	185 (6)	45 (9)	11 (5)	320 (9)	131 (13)
Incidence of cGVHD					
No	10040 (75)	1416 (79)	1231 (85)	6007 (63)	2577 (75)
Yes	2897 (22)	335 (19)	135 (9)	3081 (32)	716 (21)
Missing	525 (4)	52 (3)	74 (5)	450 (5)	139 (4)
Maximum grade of cGVHD					
Limited	1053 (36)	130 (39)	51 (38)	742 (24)	325 (45)
Extensive	1745 (60)	204 (61)	73 (54)	2228 (72)	372 (52)
Missing	99 (3)	1 (<1)	11 (8)	111 (4)	19 (3)
Overall severity of cGVHD					
Mild	1321 (46)	165 (49)	60 (44)	1132 (37)	397 (55)

Accrual Table 2. Non-leukemia patients:	HLA-identical sibling	Haplo identical	Other related	Unrelated donor	Cord blood
Moderate	936 (32)	104 (31)	39 (29)	870 (28)	188 (26)
Severe	527 (18)	60 (18)	23 (17)	686 (22)	106 (15)
Missing	113 (4)	6 (2)	13 (10)	393 (13)	25 (3)
Year of transplant					
1990-1994	2785 (21)	216 (12)	145 (10)	577 (6)	23 (1)
1995-1999	3138 (23)	206 (11)	249 (17)	1168 (12)	205 (6)
2000-2004	3457 (26)	139 (8)	255 (18)	2450 (26)	527 (15)
2005-2009	2031 (15)	145 (8)	275 (19)	2796 (29)	1092 (32)
2010-2014	606 (5)	239 (13)	212 (15)	1047 (11)	991 (29)
2015-2019	1445 (11)	858 (48)	304 (21)	1500 (16)	594 (17)
Follow-up of survivors, months, median (range)	89 (<1-340)	35 (1-337)	64 (<1-336)	88 (<1-339)	72 (<1-291)

Abbreviations: NHL=Non-Hodgkin lymphoma, HD=Hodgkin disease, SAA=Severe aplastic anemia, MM=Multiple myeloma, SCID=Severe combined immunodeficiency, Cy=Cyclophosphamide, Tac=Tacrolimus, MTX=Methotrexate, MMF=Mycophenolate mofetil, CsA=Cyclosporine, UGI=Upper gastrointestinal, LGI=Lower gastrointestinal.

Unrelated Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired samples, recipient only samples and donor only samples

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**19840**	**6243**	**3730**
Source of data			
CRF	10086 (51)	2629 (42)	2054 (55)
TED	9754 (49)	3614 (58)	1676 (45)
Number of centers	234	203	318
Disease at transplant			
AML	13566 (68)	4431 (71)	2418 (65)
ALL	5866 (30)	1674 (27)	1232 (33)
Other acute leukemia	408 (2)	138 (2)	80 (2)
AML Disease status at transplant			
CR1	6997 (52)	2391 (54)	1108 (46)
CR2	2700 (20)	841 (19)	499 (21)
CR3+	259 (2)	73 (2)	53 (2)
Advanced or active disease	3459 (26)	1085 (24)	707 (29)
Missing	147 (1)	41 (1)	47 (2)
ALL Disease status at transplant			
CR1	2842 (48)	871 (52)	516 (42)
CR2	1699 (29)	456 (27)	358 (29)
CR3+	482 (8)	127 (8)	118 (10)
Advanced or active disease	798 (14)	206 (12)	206 (17)
Missing	45 (1)	14 (1)	33 (3)
Recipient age at transplant			
0-9 years	1483 (7)	396 (6)	382 (10)
10-19 years	2015 (10)	546 (9)	493 (13)
20-29 years	2456 (12)	717 (11)	526 (14)
30-39 years	2365 (12)	689 (11)	504 (14)
40-49 years	3046 (15)	938 (15)	562 (15)
50-59 years	3787 (19)	1162 (19)	613 (16)
60-69 years	3880 (20)	1444 (23)	553 (15)
70+ years	808 (4)	351 (6)	97 (3)
Median (Range)	46 (0-84)	48 (0-79)	39 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	16459 (86)	5194 (86)	2708 (84)
African-American, non-Hispanic	746 (4)	226 (4)	149 (5)
Asian, non-Hispanic	479 (3)	203 (3)	138 (4)
Pacific islander, non-Hispanic	25 (<1)	8 (<1)	10 (<1)
Native American, non-Hispanic	77 (<1)	25 (<1)	17 (1)
Hispanic	1330 (7)	370 (6)	195 (6)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Other	18 (<1)	11 (<1)	10 (<1)
Unknown	706 (N/A)	206 (N/A)	503 (N/A)
Recipient sex			
Male	10967 (55)	3463 (55)	2121 (57)
Female	8873 (45)	2780 (45)	1609 (43)
Karnofsky score			
10-80	6977 (35)	2349 (38)	1164 (31)
90-100	12133 (61)	3594 (58)	2279 (61)
Missing	730 (4)	300 (5)	287 (8)
HLA-A B DRB1 groups - low resolution			
<=3/6	14 (<1)	23 (<1)	0
4/6	95 (<1)	45 (1)	17 (<1)
5/6	2778 (14)	742 (14)	563 (16)
6/6	16691 (85)	4620 (85)	2925 (83)
Unknown	262 (N/A)	813 (N/A)	225 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	376 (2)	55 (1)	21 (1)
6/8	828 (4)	64 (1)	61 (3)
7/8	3925 (20)	774 (18)	546 (23)
8/8	14038 (73)	3422 (79)	1716 (73)
Unknown	673 (N/A)	1928 (N/A)	1386 (N/A)
HLA-DPB1 Match			
Double allele mismatch	4898 (30)	442 (26)	198 (29)
Single allele mismatch	8797 (53)	840 (50)	361 (53)
Full allele matched	2763 (17)	393 (23)	123 (18)
Unknown	3382 (N/A)	4568 (N/A)	3048 (N/A)
High resolution release score			
No	5274 (27)	6182 (99)	3649 (98)
Yes	14566 (73)	61 (1)	81 (2)
KIR typing available			
No	11326 (57)	6202 (99)	3707 (99)
Yes	8514 (43)	41 (1)	23 (1)
Graft type			
Marrow	6849 (35)	1953 (31)	1531 (41)
PBSC	12970 (65)	4205 (67)	2191 (59)
BM+PBSC	4 (<1)	5 (<1)	1 (<1)
PBSC+UCB	13 (<1)	73 (1)	2 (<1)
Others	4 (<1)	7 (<1)	5 (<1)
Number of cord blood units			
1	6 (100)	0	1 (100)
Conditioning regimen			
Myeloablative	14399 (73)	4267 (68)	2784 (75)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
RIC/Nonmyeloablative	5361 (27)	1960 (31)	893 (24)
TBD	80 (<1)	16 (<1)	53 (1)
Donor age at donation			
To Be Determined/NA	118 (1)	720 (12)	34 (1)
0-9 years	4 (<1)	17 (<1)	1 (<1)
10-19 years	585 (3)	202 (3)	85 (2)
20-29 years	9024 (45)	2566 (41)	1447 (39)
30-39 years	5542 (28)	1586 (25)	1140 (31)
40-49 years	3476 (18)	885 (14)	783 (21)
50+ years	1091 (5)	267 (4)	240 (6)
Median (Range)	30 (0-61)	30 (0-73)	33 (7-67)
Donor/Recipient CMV serostatus			
+/+	5149 (26)	1807 (30)	940 (26)
+/-	2207 (11)	731 (12)	457 (13)
-/+	7025 (36)	2039 (34)	1220 (34)
-/-	5167 (26)	1440 (24)	934 (26)
CB - recipient +	1 (<1)	6 (<1)	0
CB - recipient -	0	2 (<1)	0
CB - recipient CMV unknown	0	1 (<1)	0
Unknown	291 (N/A)	217 (N/A)	179 (N/A)
GvHD Prophylaxis			
Ex vivo T-cell depletion	549 (3)	140 (2)	162 (4)
CD34 selection	318 (2)	134 (2)	59 (2)
Post-CY + other(s)	557 (3)	334 (5)	61 (2)
Post-CY alone	53 (<1)	22 (<1)	12 (<1)
Tacrolimus + MMF +- others	2160 (11)	656 (11)	251 (7)
Tacrolimus + MTX +- others (except MMF)	9470 (48)	2994 (48)	1152 (31)
Tacrolimus + others (except MTX, MMF)	1067 (5)	403 (6)	151 (4)
Tacrolimus alone	494 (2)	171 (3)	64 (2)
CSA + MMF +- others (except Tacrolimus)	1036 (5)	266 (4)	246 (7)
CSA + MTX +- others (except Tacrolimus, MMF)	3047 (15)	785 (13)	1167 (31)
CSA + others (except Tacrolimus, MTX, MMF)	320 (2)	106 (2)	125 (3)
CSA alone	221 (1)	69 (1)	149 (4)
Other GVHD prophylaxis	313 (2)	96 (2)	61 (2)
Missing	235 (1)	67 (1)	70 (2)
Donor/Recipient sex match			
Male-Male	7780 (39)	2338 (38)	1403 (38)
Male-Female	5391 (27)	1640 (27)	933 (25)
Female-Male	3117 (16)	1051 (17)	694 (19)
Female-Female	3425 (17)	1060 (17)	654 (18)
CB - recipient M	5 (<1)	38 (1)	0
CB - recipient F	8 (<1)	40 (1)	2 (<1)

Accrual Table 3. **Unrelated donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	114 (N/A)	76 (N/A)	44 (N/A)
Year of transplant			
1986-1990	119 (1)	17 (<1)	32 (1)
1991-1995	708 (4)	189 (3)	255 (7)
1996-2000	1322 (7)	474 (8)	431 (12)
2001-2005	2476 (12)	516 (8)	738 (20)
2006-2010	4577 (23)	958 (15)	753 (20)
2011-2015	6635 (33)	1835 (29)	926 (25)
2016-2019	4003 (20)	2254 (36)	595 (16)
Follow-up among survivors, Months			
N Eval	8242	2943	1391
Median (Range)	50 (1-338)	26 (1-325)	47 (1-350)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Unrelated Cord Blood Transplant Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and cord blood only samples

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3250**	**756**	**720**
Source of data			
CRF	2419 (74)	569 (75)	484 (67)
TED	831 (26)	187 (25)	236 (33)
Number of centers	137	115	158
Disease at transplant			
AML	2044 (63)	451 (60)	409 (57)
ALL	1121 (34)	287 (38)	289 (40)
Other acute leukemia	85 (3)	18 (2)	22 (3)
AML Disease status at transplant			
CR1	1048 (51)	242 (54)	199 (49)
CR2	569 (28)	114 (25)	116 (28)
CR3+	50 (2)	6 (1)	12 (3)
Advanced or active disease	370 (18)	86 (19)	80 (20)
Missing	7 (<1)	2 (<1)	2 (<1)
ALL Disease status at transplant			
CR1	507 (45)	122 (43)	130 (45)
CR2	421 (38)	108 (38)	103 (36)
CR3+	120 (11)	39 (14)	31 (11)
Advanced or active disease	72 (6)	18 (6)	25 (9)
Missing	1 (<1)	0	0
Recipient age at transplant			
0-9 years	724 (22)	228 (30)	189 (26)
10-19 years	477 (15)	112 (15)	130 (18)
20-29 years	376 (12)	60 (8)	69 (10)
30-39 years	363 (11)	80 (11)	83 (12)
40-49 years	372 (11)	76 (10)	75 (10)
50-59 years	470 (14)	92 (12)	89 (12)
60-69 years	410 (13)	94 (12)	79 (11)
70+ years	58 (2)	14 (2)	6 (1)
Median (Range)	31 (0-83)	27 (0-77)	25 (0-78)
Recipient race/ethnicity			
Caucasian, non-Hispanic	1820 (59)	440 (62)	401 (63)
African-American, non-Hispanic	411 (13)	88 (12)	72 (11)
Asian, non-Hispanic	202 (7)	45 (6)	52 (8)
Pacific islander, non-Hispanic	20 (1)	3 (<1)	7 (1)
Native American, non-Hispanic	18 (1)	3 (<1)	6 (1)
Hispanic	606 (20)	136 (19)	100 (16)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	173 (N/A)	41 (N/A)	82 (N/A)
Recipient sex			
Male	1715 (53)	408 (54)	402 (56)
Female	1535 (47)	348 (46)	318 (44)
Karnofsky score			
10-80	872 (27)	198 (26)	173 (24)
90-100	2313 (71)	526 (70)	515 (72)
Missing	65 (2)	32 (4)	32 (4)
HLA-A B DRB1 groups - low resolution			
<=3/6	45 (1)	24 (4)	6 (1)
4/6	1384 (44)	259 (44)	262 (39)
5/6	1349 (43)	227 (39)	321 (48)
6/6	337 (11)	73 (13)	78 (12)
Unknown	135 (N/A)	173 (N/A)	53 (N/A)
High-resolution HLA matches available out of 8			
<=5/8	1601 (59)	258 (60)	299 (55)
6/8	650 (24)	97 (23)	136 (25)
7/8	330 (12)	43 (10)	79 (15)
8/8	150 (5)	29 (7)	29 (5)
Unknown	519 (N/A)	329 (N/A)	177 (N/A)
HLA-DPB1 Match			
Double allele mismatch	425 (39)	38 (47)	36 (40)
Single allele mismatch	559 (52)	35 (43)	43 (48)
Full allele matched	99 (9)	8 (10)	11 (12)
Unknown	2167 (N/A)	675 (N/A)	630 (N/A)
High resolution release score			
No	2436 (75)	724 (96)	714 (99)
Yes	814 (25)	32 (4)	6 (1)
KIR typing available			
No	2566 (79)	751 (99)	715 (99)
Yes	684 (21)	5 (1)	5 (1)
Number of cord blood units			
1	2665 (82)	0	587 (82)
2	584 (18)	0	133 (18)
3	1 (<1)	0	0
Unknown	0 (N/A)	756 (N/A)	0 (N/A)
Graft type			
UCB	3070 (94)	683 (90)	675 (94)
PBSC+UCB	161 (5)	73 (10)	39 (5)
Others	19 (1)	0	6 (1)
Conditioning regimen			
Myeloablative	2301 (71)	542 (72)	498 (69)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
RIC/Nonmyeloablative	943 (29)	212 (28)	221 (31)
TBD	6 (<1)	2 (<1)	1 (<1)
Donor age at donation			
To Be Determined/NA	99 (3)	41 (5)	41 (6)
0-9 years	2899 (89)	587 (78)	620 (86)
10-19 years	147 (5)	67 (9)	29 (4)
20-29 years	32 (1)	20 (3)	6 (1)
30-39 years	32 (1)	22 (3)	12 (2)
40-49 years	17 (1)	9 (1)	4 (1)
50+ years	24 (1)	10 (1)	8 (1)
Median (Range)	3 (0-72)	5 (0-73)	3 (0-72)
Donor/Recipient CMV serostatus			
+/+	838 (26)	167 (22)	155 (22)
+/-	292 (9)	76 (10)	56 (8)
-/+	644 (20)	142 (19)	148 (21)
-/-	378 (12)	78 (10)	97 (13)
CB - recipient +	707 (22)	181 (24)	146 (20)
CB - recipient -	352 (11)	90 (12)	101 (14)
CB - recipient CMV unknown	39 (1)	22 (3)	17 (2)
GvHD Prophylaxis			
Ex vivo T-cell depletion	21 (1)	6 (1)	2 (<1)
CD34 selection	133 (4)	57 (8)	34 (5)
Post-CY + other(s)	3 (<1)	3 (<1)	0
Tacrolimus + MMF +- others	905 (28)	196 (26)	115 (16)
Tacrolimus + MTX +- others (except MMF)	127 (4)	36 (5)	37 (5)
Tacrolimus + others (except MTX, MMF)	107 (3)	29 (4)	18 (3)
Tacrolimus alone	73 (2)	20 (3)	10 (1)
CSA + MMF +- others (except Tacrolimus)	1596 (49)	328 (43)	385 (53)
CSA + MTX +- others (except Tacrolimus, MMF)	53 (2)	13 (2)	18 (3)
CSA + others (except Tacrolimus, MTX, MMF)	123 (4)	46 (6)	60 (8)
CSA alone	30 (1)	9 (1)	27 (4)
Other GVHD prophylaxis	64 (2)	5 (1)	11 (2)
Missing	15 (<1)	8 (1)	3 (<1)
Donor/Recipient sex match			
CB - recipient M	1715 (53)	408 (54)	400 (56)
CB - recipient F	1535 (47)	348 (46)	318 (44)
CB - recipient sex unknown	0	0	2 (<1)
Year of transplant			
1996-2000	0	1 (<1)	3 (<1)
2001-2005	51 (2)	53 (7)	15 (2)
2006-2010	1016 (31)	224 (30)	222 (31)
2011-2015	1528 (47)	268 (35)	344 (48)

Accrual Table 4. **Unrelated cord blood research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
2016-2019	655 (20)	210 (28)	136 (19)
Follow-up among survivors, Months			
N Eval	1494	381	330
Median (Range)	52 (2-168)	44 (3-192)	48 (1-176)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

Related Donor HCT Research Sample Inventory - Summary for First Allogeneic Transplants in CRF and TED with biospecimens available through the CIBMTR Repository stratified by availability of paired, recipient only and donor only samples

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Number of patients	**3840**	**598**	**226**
Source of data			
CRF	1224 (32)	145 (24)	83 (37)
TED	2616 (68)	453 (76)	143 (63)
Number of centers	80	60	42
Disease at transplant			
AML	2519 (66)	367 (61)	140 (62)
ALL	1219 (32)	215 (36)	83 (37)
Other acute leukemia	102 (3)	16 (3)	3 (1)
AML Disease status at transplant			
CR1	1570 (62)	243 (66)	86 (61)
CR2	391 (16)	42 (11)	15 (11)
CR3+	28 (1)	6 (2)	1 (1)
Advanced or active disease	520 (21)	73 (20)	36 (26)
Missing	10 (<1)	3 (1)	2 (1)
ALL Disease status at transplant			
CR1	765 (63)	136 (63)	56 (67)
CR2	326 (27)	49 (23)	16 (19)
CR3+	62 (5)	9 (4)	6 (7)
Advanced or active disease	66 (5)	20 (9)	5 (6)
Missing	0	1 (<1)	0
Recipient age at transplant			
0-9 years	257 (7)	29 (5)	10 (4)
10-19 years	408 (11)	43 (7)	23 (10)
20-29 years	381 (10)	76 (13)	27 (12)
30-39 years	385 (10)	61 (10)	24 (11)
40-49 years	566 (15)	101 (17)	33 (15)
50-59 years	875 (23)	135 (23)	44 (19)
60-69 years	838 (22)	132 (22)	57 (25)
70+ years	130 (3)	21 (4)	8 (4)
Median (Range)	49 (1-78)	49 (1-76)	49 (2-77)
Recipient race/ethnicity			
Caucasian, non-Hispanic	2475 (68)	317 (57)	148 (69)
African-American, non-Hispanic	344 (9)	45 (8)	11 (5)
Asian, non-Hispanic	170 (5)	58 (10)	11 (5)
Pacific islander, non-Hispanic	11 (<1)	1 (<1)	1 (<1)
Native American, non-Hispanic	16 (<1)	1 (<1)	0
Hispanic	634 (17)	136 (24)	42 (20)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
Unknown	190 (N/A)	40 (N/A)	13 (N/A)
Recipient sex			
Male	2178 (57)	339 (57)	126 (56)
Female	1662 (43)	259 (43)	100 (44)
Karnofsky score			
10-80	1429 (37)	274 (46)	93 (41)
90-100	2332 (61)	314 (53)	124 (55)
Missing	79 (2)	10 (2)	9 (4)
Graft type			
Marrow	973 (25)	115 (19)	63 (28)
PBSC	2853 (74)	476 (80)	159 (70)
BM+PBSC	2 (<1)	3 (1)	0
BM+UCB	4 (<1)	1 (<1)	0
PBSC+UCB	0	0	3 (1)
Others	8 (<1)	3 (1)	1 (<1)
Conditioning regimen			
Myeloablative	2704 (70)	408 (68)	156 (69)
RIC/Nonmyeloablative	1130 (29)	188 (31)	68 (30)
TBD	6 (<1)	2 (<1)	2 (1)
Donor age at donation			
To Be Determined/NA	8 (<1)	1 (<1)	0
0-9 years	182 (5)	18 (3)	11 (5)
10-19 years	353 (9)	50 (8)	17 (8)
20-29 years	555 (14)	96 (16)	29 (13)
30-39 years	567 (15)	108 (18)	40 (18)
40-49 years	624 (16)	106 (18)	31 (14)
50+ years	1551 (40)	219 (37)	98 (43)
Median (Range)	44 (0-80)	43 (0-79)	45 (3-76)
Donor/Recipient CMV serostatus			
+/+	1259 (42)	252 (53)	89 (51)
+/-	286 (10)	31 (7)	15 (9)
-/+	862 (29)	118 (25)	45 (26)
-/-	558 (19)	75 (16)	27 (15)
Unknown	42 (N/A)	5 (N/A)	5 (N/A)
GvHD Prophylaxis			
Ex-vivo T-cell depletion	56 (1)	16 (3)	4 (2)
CD34 selection	59 (2)	14 (2)	6 (3)
Post-CY + other(s)	848 (22)	126 (21)	53 (23)
Post-CY alone	24 (1)	7 (1)	3 (1)
TAC + MMF +- other(s) (except post-CY)	350 (9)	32 (5)	16 (7)
TAC + MTX +- other(s) (except MMF, post-CY)	1683 (44)	194 (32)	96 (42)
TAC + other(s) (except MMF, MTX, post-CY)	341 (9)	150 (25)	22 (10)

Accrual Table 5. **Related donor research sample:**	Samples Available for Recipient and Donor N (%)	Samples Available for Recipient Only N (%)	Samples Available for Donor Only N (%)
TAC alone	21 (1)	1 (<1)	2 (1)
CSA + MMF +- other(s) (except post-CY)	54 (1)	7 (1)	3 (1)
CSA + MTX +- other(s) (except MMF, post-CY)	280 (7)	29 (5)	15 (7)
CSA + others (except TAC, MTX, MMF, post-CY)	0	1 (<1)	0
CSA alone	31 (1)	6 (1)	0
Other(s)	38 (1)	7 (1)	3 (1)
Missing	55 (1)	8 (1)	3 (1)
Donor/Recipient sex match			
Male-Male	1225 (32)	215 (36)	67 (30)
Male-Female	866 (23)	132 (22)	52 (23)
Female-Male	950 (25)	122 (20)	57 (25)
Female-Female	795 (21)	125 (21)	46 (20)
CB - recipient M	3 (<1)	2 (<1)	2 (1)
CB - recipient F	1 (<1)	2 (<1)	2 (1)
Year of transplant			
2006-2010	249 (6)	26 (4)	19 (8)
2011-2015	1757 (46)	254 (42)	86 (38)
2016-2019	1834 (48)	318 (53)	121 (54)
Follow-up among survivors, Months			
N Eval	2318	355	135
Median (Range)	25 (2-124)	24 (3-101)	25 (3-120)

Abbreviations: CRF=Comprehensive report form, TED=Transplant essential data, AML=Acute myelogenous leukemia, ALL=Acute lymphoblastic leukemia, UCB=Umbilical cord blood, BM=Bone marrow, PBSC=Peripheral blood stem cells, RIC=Reduced intensity conditioning, TBD=To be determined, NA=Not applicable, Post-CY=Post-transplant Cyclophosphamide, TAC=Tacrolimus, MMF=Mycophenolate mofetil, MTX=Methotrexate, CsA=Cyclosporine.

* Biospecimens include: whole blood, serum/plasma and limited quantities of viable cells and cell lines (collected prior to 2006). Specific inventory queries available upon request through the CIBMTR Immunobiology Research Program

CIBMTR®
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

TO: Graft-Versus-Host Disease Working Committee Members

FROM: Mukta Arora, MD, MS and Stephen Spellman, MBS; Scientific Directors for GVWC

RE: Studies in Progress Summary

GV17-01: Investigating antibiotic exposure and risk of acute GVHD in children undergoing HCT for acute leukemia (C Elgarten/ B Fisher/ R Aplenc)
This study aims to determine the association and impact of pre-transplant antibiotic exposures with subsequent development of aGVHD in pediatric leukemia patients. The hypothesis is that exposure to antibiotics with activity against anaerobic commensal microorganisms during the pre- and peri-transplant time periods will be associated with an increased risk of aGVHD. The study involved merging data between the CIBMTR and Pediatric Health Information System (PHIS) databases. The initial results were presented at the CIBMTR Statistical Meeting in July 2019. These results were presented as an oral presentation at ASH in December 2019. An initial manuscript draft has been received for review and the plan is to submit for publication by May 2020.

GV17-03: Alterations in the characteristics and outcomes of GVHD following post-transplant Cy for haploidentical HCT and in patients over 60 at high risk for GVHD (R Saliba/ S Ciurea/ J Schriber)
This study aims to compare GVHD and other post GVHD outcomes between recipients of PT-Cy-based haploidentical HCT versus 8/8-matched unrelated donor with standard GVHD prophylaxis. In addition, a subset analysis will be performed comparing PT-Cy-based versus standard GVHD prophylaxis in those > 60 years. The data file was cleaned and forwarded to Dr. Rima Saliba in June 2019. After review of the data, initial analyses were presented at the CIBMTR Statistical Meeting in October 2019. An abstract for TCT was submitted and accepted as an oral presentation. An initial manuscript is pending (with additional analysis) which is anticipated by April 2020 and a revised manuscript submitted for publication by June 2020.

GV18-01: Comparison of late effects among allogeneic hematopoietic cell transplantation survivors with and without chronic graft-versus-host disease (Lee CJ/ Couriel DR)
This study aims to compare the cumulative incidence of late effects between one-year survivors of allogeneic HCT diagnosed with chronic GVHD versus those without chronic GVHD. Furthermore, the effects of chronic GVHD onset, severity and organ involvement on late effects will be evaluated. The draft protocol was received in August 2019. The plan is to present the protocol at the CIBMTR Statistical Meeting in early Spring 2020. Following approval, the protocol will be forwarded to form a Writing Committee and the data file will be prepared for analysis by June 2020.

GV18-02: Comparison of antibacterial prophylaxis strategies and outcomes in allogeneic hematopoietic cell transplantation patients with acute graft-versus-host disease (Wallis W/ Alousi AM/ Gulbis A)
This study aims to determine the incidence of bacterial bloodstream infections (BSI) in patients with acute GVHD II-IV. The initial protocol was discussed in more detail with the principal investigators in July

2019. In August 2019, an existing finalized dataset from the CIBMTR's Infection Working Committee was found to be a suitable data source to address the questions posed in **GV18-02**. These data were evaluated more closely in October 2019 and will be presented at the CIBMTR Statistical Meeting in Spring 2020. After approval, the protocol will be forwarded to form a Writing Committee.

GV18-03: Impact of chronic graft-versus-host disease on non-relapse mortality and disease relapse in transplant recipients (Bhatt V/ Lee SJ)
This study aims to compare non-relapse morality and disease relapse of older transplant recipients (≥40 years old) who experience post-HCT GVHD versus those who do not experience chronic GVHD. Further aims will be to determine the impact of baseline characteristics on chronic GVHD incidence, as well as the impact of chronic GVHD on non-relapse mortality and relapse among older patients (≥70 years old). The draft protocol was received in November 2019. The plan is to present the protocol at the CIBMTR Statistical Meeting in Spring 2020. Following approval, the protocol will be forwarded to form a Writing Committee and the data file will be prepared for analysis by June 2020.

GV19-01: Exploring the link between donor-engrafted clonal hematopoiesis and adverse outcomes in allogeneic hematopoietic cell transplant recipients (Gillis N/ Padron E/ Lazaryan A)
This study aims to compare allo-HCT outcomes between recipients with older (≥ 55 years old) HLA-matched related donors without clonal hematopoiesis and recipients with young (< 25 years old) HLA-matched unrelated donors. Next-generation sequencing will be used to determine the prevalence of clonal hematopoiesis in the older donor samples obtained from the CIBMTR research sample repository. The draft protocol was presented at the CIBMTR Statistical Meeting in September 2019 and sample typing will be completed in January 2020. The plan is to forward the protocol to form a Writing Committee and complete data file preparation by Spring 2020.

Combined Proposal: 1911-80/1911-175

Title:
Determining the optimal anti-thymocyte globulin dosing in patients with hematologic malignancies.

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Research hypothesis:
The appropriate dose of ATG added to the allogenic transplantation regimen based on conditioning intensity, donor choice (MRD, MUD, MMUD, haploidentical, CB) stem cell source (BM, PB) and risk factors for acute graft versus host disease (GVHD), would decrease the incidence of GVHD without significantly increasing the risk of infection and relapse

Specific aims:
We propose a retrospective analysis of patients who underwent allogenic transplantation to evaluate association between the dose of antithymocyte globulin (ATG) and outcomes
Primary aim:

- To determine the optimal dose of ATG in patients who underwent matched related donor (MRD), matched unrelated donor (MUD), mismatched unrelated donor (MMUD), CB, or haploidentical, transplant with myeloabliative (MAC), or reduced intensity (RIC) / non-myeloablative (NMA) conditioning.

Secondary aim:

- Comparison of one year graft versus host disease (GVHD), disease relapse, GVHD-free Relapse-free Survival (GRFS), progression free survival (PFS) and overall survival (OS) among different doses of ATG
- To determine the cumulative incidence of grade II-IV acute GVHD (aGVHD) at day 100 and 180.
- To determine 100 days, 1 year and 2 year cumulative incidence of treatment-related mortality (TRM)
- To determine the cumulative incidence of chronic GVHD (cGVHD)
- To determine hematologic recovery (neutrophil and platelet), toxicity and rates of infection
- Identify whether patients with established risk factors for acute GVHD benefit from higher ATG dosing than patients without risk factors for acute GVHD.

Scientific impact:
Allogenic hematopoietic stem cell transplantation is increasingly used as a treatment for patients with life threatening blood diseases. The success of this is based on immune-based graft versus leukemia effect caused by donor T cells. But donor T-cells are also the cause of GVHD. These observations have led to various studies aiming at assessing the impact of immunoregulation with ATG on transplantation outcomes. Adding ATG in one of its three commercially available preparations (Thymoglobulin, ATGAM, and ATG-Fresenius) for in vivo T- cell depletion has been shown to decrease the incidence of aGVHD and

cGVHD, with mixed effects on disease relapse [1-7]. However, due to the differences in preparations and dose of ATG, it has been difficult to compare outcomes between them [1]. Currently in the United State, thymoglobulin (ATG-T) is utilized with dose range of 2.5-10mg/kg. In Europe, Neovii/Grafalon (ATG-F) is utilized as well, with a range of 15-60mg/kg. For the purposes of this study we will be dealing with ATG-T, only. This study will utilize CIBMTR data to define the appropriate dose, schedule, and preparation of ATG-T that should be added to GVHD prophylaxis regimens to improve transplantation outcomes in patients given stem cells from either antigen matched related or unrelated donors or mismatched donors. This analysis would have a huge impact across the centers in improving patient outcomes after allo-HSCT.

Scientific justification:

Acute graft versus host disease has been, and continues to compromise the benefits associated with allogeneic hematopoietic cell transplantation to cure malignant and non-malignant diseases. Pharmacologic interventions to prevent GVHD have emerged as a major objective of research in the immunology and transplantation fields. A better understanding of the pathobiology behind the GVHD process has led the way to novel approaches and medications. To this end, the role of ATG in preventing aGVHD has been explored in the past but still remains controversial. ATG has been incorporated in standard GVHD prophylaxis regimens. ATG works through multiple mechanisms including T-cell depletion in the blood and lymphoid tissues by induction of apoptosis or complement-dependent lysis, apoptosis of naïve B cells, activated B-cells and plasma cells [2, 3], and by induction of regulatory T-cells, and natural killer (NK) cells [4]. These effects could potentially lead to serious infections such as (cytomegalovirus) CMV and (Epstein-Barr virus) EBV, and possibly to disease relapse [5-7]. Comparisons between ATG doses of 6mgk/kg vs. 7.5mg/kg in the RIC setting showed no significant difference in acute or chronic GVHD, NRM, relapse, PFS, and OS between groups [8]. Recently, we reported aGVHD incidence to be higher at 4.5mg/kg versus 6mg/kg. However, the difference in incidence was not statistically significant[9]. But, there was a significantly decreased risk in the incidence of CMV and EBV reactivation at 180 days in the 4.5mg/kg group compared to the 6mg/kg group. Several studies have tried to define the appropriate dose, schedule, and preparation of ATG that should be added based on the conditioning intensity, donor choice and other risk factors to decrease the incidence of GVHD, without significantly increasing the risk of infection and relapse [10-13]. To date, a large scale analysis to identify the optimal dose of ATG-T has not yet been undertaken. Given the heterogeneity of the patients undergoing HCT, there may not be a single, optimal dose. Instead, ATG-T dosing may depend on intensity of the preparative regimen, donor characteristics, and recipient lymphocyte counts. The number of patients required to retrospectively determine the dosing of ATG-T in relation to these characteristics would be too significant for any one institution to undertake. The CIBMTR dataset would allow such an analysis to occur. This type of study could potentially inform ATG-T dosing as well as the design of a prospective analysis with personalized ATG-T dosing. The proposed study is an ongoing quality improvement effort to define the appropriate dose, schedule, and preparation of ATG that should be added to GVHD prophylaxis regimens to decrease the incidence of GVHD, without significantly increasing the risk of infection and relapse [14].

Patient eligibility population:

Inclusion criteria:

- Patients undergoing allogenic stem cell transplantation from Jan/1/2005- Dec/31/2018
- Patients transplanted within the United States (due to the exclusive use of thymoglobulin, ATG-T)
- Age 18 to 75 years
- First HCT
- PBSC, BM or CB

- MUD, mMUD, MRD, haploidentical, CB
- Conditioning Intensity: MAC, RIC, NMA

Exclusion criteria:
- Ex-vivo T-cell depletion
- Horse ATG
- ATG doses over 15mg/kg (to eliminate those that may have received ATG-F on a clinical trial)

Data requirements:
Patient-related:
- Patient age at HCT: 18-29, 30-55, vs. 56-65, vs. 66-75
- Karnofsky performance score: ≥90 vs. <90
- HCT-CI: 0 vs. 1-2 vs. ≥3
- Race

Donor related:
- Donor age at HCT: 18-29, 30-55, vs. 56-65
- Sex
- Parity (Nulliparous vs. multiparous)

Disease-related:
- Time from diagnosis to HCT, months: < 6 vs. 6 to <12 vs. ≥ 12
- All hematological malignancies (subset analysis: Leukemia's, lymphoid malignancies)
- Disease status at transplant: CR1 ≥ CR2 < CR
- Disease risk status (including cytogenetics)

Transplant-related:
- Graft: MRD, MUD, MMUD, CB
- Stem cell source: PBSC vs. BM vs. CB
- HLA Match: 10/10 or ≤ 9/10 related, 10/10 or ≤ 9/10 unrelated, haploidentical
- Conditioning intensity: MAC vs. RIC/NMA
- ATG-T
    - Total prescribed dose (mg/kg): less than 1mg/kg, 1-2.9mg/kg, 2-3.9mg/kg, 4-4.9mg/kg, 5-6.9mg/kg, 7-9.9mg/kg, 10-15mg/kg
- TBI-based preparative regimen
- Female → Male vs. all others.
- Donor/Recipient CMV status: -/+ vs. +/- vs. +/+ vs. -/-
- GVHD prophylaxis
- Cell dose

Post-HCT data:
- CMV reactivation
- EBV reactivation
- Development of PTLD
- Graft rejection rate; primary and secondary
- Acute GVHD:

  - Overall grade at diagnosis
  - Max grade at D+100 and D+180
- Chronic GVHD:
  - Chronic GVHD at 6 months, 1 year, and 2 years
  - Max grade cGVHD (mild, moderate, severe)
  - Limited or extensive cGVHD
- Primary cause of death
  - Acute GVHD,
  - Chronic GVHD
  - Relapse/Progression of Disease
  - TRM
  - Infection
    - Not identified
    - Bacterial
    - Fungal
    - Viral
    - Protozoal
    - Other
  - Other
- Contributing cause of death
  - Acute GVHD
  - Chronic GVHD
  - Infection
    - Not identified
    - Bacterial
    - Fungal
    - Viral
    - Protozoal
    - Other
  - Other
- Overall Survival

Sample requirements:
N/A

Study design:
This is an observational study to identify the most promising ATG-T dose for patients with malignant disease. Patients will be grouped according to the dose of ATG used. We will compare the clinical and demographic variables between the cohorts of patients included in the study. The primary endpoint of GVHD/relapse of PFS post transplantation collected through the CIBMTR will be compared between the groups. Comparison among the different groups will be used to guide selection of the most promising dose for further study.

Proposed analysis:
Patients meeting the above criteria will be divided based on the dosing of ATG received less than 1mg/kg, 1-2.9mg/kg, 2-3.9mg/kg, 4-4.9mg/kg, 5-6.9mg/kg, 7-9.9mg/kg, 10-15mg/kg. Descriptive statistics will be used to describe the characteristics of the patients in each group (i.e., conditioning

intensity, graft characteristics, and other known risk factors for aGVHD). Next, the incidence and maximum grade of acute GVHD by the Glucksberg grading system will be determined for each of the groups and summarized by cumulative incidence probability, where death without aGVHD will be treated as a competing risk and reported with 95% confidence intervals. Cox proportional hazard models will assess the impact of aGVHD and infectious complications on TRM. In instances where aGVHD and infection is listed as both the primary and contributing cause of death (or the opposite), only the primary causes of death will be counted. OS calculations using Kaplan-Meier curves will be performed in each of the groups with median OS calculated for each of the five groups.
The following established risk factors for aGVHD will be assessed: TBI-based preparative regimen, ablative conditioning regimen, F → M donor, mMUD, and PBSCs will be assessed for each patient. Patients with 0-1 risks, 2 risks, and ≥ 3 risks factors will first have their incidence and max grade of aGVHD calculated to confirm that increasing risk factors are associated with a higher incidence of aGVHD. Patients in these groups will then be divided based on ATG dosing at less than 1mg/kg, 1-2.9mg/kg, 2-3.9mg/kg, 4-4.9mg/kg, 5-6.9mg/kg, 7-9.9mg/kg, 10-15mg/kg with the cumulative incidence and max grade of aGVHD, TRM, and OS calculated in each group, as described above.

Non-CIBMTR data source:
N/A

Conflicts of interest:
No

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Characteristics of adult patients receiving first allo-HCT for hematologic malignancy with rabbit ATG in the United States from 2005-2018, as reported to the CIBMTR

Characteristic	N (%)
No. of patients	4468
No. of centers	138
Age at HCT	
Median (min-max)	55.61 (18.01-74.98)
18-29	456 (10.2)
30-39	430 (9.6)
40-49	690 (15.4)
50-59	1275 (28.5)
60-69	1402 (31.4)
≥70	215 (4.8)
Gender	
Male	2586 (57.9)
Female	1882 (42.1)
Disease	
AML	1794 (40.2)
ALL	379 (8.5)
Other leukemia	200 (4.5)
CML	171 (3.8)
MDS	1302 (29.1)
Other acute leukemia	28 (0.6)
NHL	417 (9.3)
HD	124 (2.8)
PCD/MM	53 (1.2)
Donor type	
HLA-identical sibling	504 (11.3)
Haploidentical	67 (1.5)
Well-matched unrelated (8/8)	2369 (53)
Partially-matched unrelated (7/8)	779 (17.4)
Mis-matched unrelated (≤6/8)	75 (1.7)
Cord blood	674 (15.1)
Graft type	
Bone marrow	573 (12.8)
Peripheral blood	3221 (72.1)
Cord blood	674 (15.1)
Rabbit ATG dose (mg/kg)	
Median (min-max)	4.5 (0.01-15)
<1	169 (3.8)
1-1.9	97 (2.2)

Characteristic	N (%)
2-2.9	353 (7.9)
3-3.9	614 (13.7)
4-4.9	833 (18.6)
5-5.9	474 (10.6)
6-6.9	389 (8.7)
7-7.9	241 (5.4)
8-8.9	40 (0.9)
9-9.9	16 (0.4)
≥10	25 (0.6)
Missing	1217 (27.2)
GVHD prophylaxis	
No GVHD prophylaxis	46 (1)
CD34 selection	291 (6.5)
Post-CY + other(s)	29 (0.6)
TAC + MMF ± other(s) (except post-CY)	1212 (27.1)
TAC + MTX ± other(s) (except MMF, post-CY)	1978 (44.3)
TAC + other(s) (except MMF, MTX, post-CY)	229 (5.1)
TAC alone	102 (2.3)
CSA + MMF ± other(s) (except post-CY)	371 (8.3)
CSA + MTX ± other(s) (except MMF, post-CY)	102 (2.3)
CSA + other(s) (except MMF, MTX, post-CY)	18 (0.4)
CSA alone	27 (0.6)
Other(s)	34 (0.8)
Missing	29 (0.6)
Conditioning regimen intensity	
MAC	2086 (46.7)
RIC	1879 (42.1)
NMA	401 (9)
TBD	79 (1.8)
Missing	23 (0.5)
Year of HCT	
2005	345 (7.7)
2006	375 (8.4)
2007	458 (10.3)
2008	456 (10.2)
2009	473 (10.6)
2010	312 (7)
2011	248 (5.6)
2012	250 (5.6)
2013	365 (8.2)
2014	376 (8.4)

Characteristic	N (%)
2015	282 (6.3)
2016	228 (5.1)
2017	191 (4.3)
2018	109 (2.4)
Follow-up of survivors, months - median (min-max)	96.05 (3.29-173.98)

Proposal: 1911-52

Title:
HLA-DQ2/DQ8 and GVHD risk in pediatric patients undergoing hematopoietic stem cell transplant

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Research hypothesis:
HLA-DQ2 and DQ8 are strongly associated with celiac disease (CD) in the general population; however, several small studies have shown them to be protective against inflammatory bowel disease (IBD). Based on our preliminary data, we hypothesize these genotypes will have a protective effect against clinically significant and severe graft-versus-host disease (GVHD) in a dose-dependent manner.

Specific aims:
- Establish the predictive value of HLA-DQ2 and DQ8 genotypes for GVHD risk in children
    - We will evaluate time to any clinically significant (grade ≥2 acute or any chronic) or severe (grade ≥3 or chronic extensive) GVHD by genetic risk factors
    - We will compare rates of acute and chronic GVHD and target organs by genetic risks
- Evaluate the effects of these genotypes on major transplant outcomes
    - We will measure overall and event-free survival, transplant-related mortality (TRM) and primary and secondary graft failure in all patients by genetic risk
    - We will estimate relapse risk and GVHD/relapse-free survival among children with malignant transplant indications by genetic risk

Scientific impact:
Identification of a potential GVHD risk modifier may identify patients who are able to tolerate faster reduction of immunosuppression, which is particularly important for children with leukemia. Of note, in our pilot data, high and moderate celiac risk genotypes were enriched in children with malignant transplant indications.

Scientific justification:
GVHD causes significant morbidity and mortality after allogeneic stem cell transplant (SCT). Little is known about genetic determinants of GVHD risk, including human leukocyte antigen (HLA) genotypes outside of HLA-mismatch. HLA-DQ2 and DQ8 genotypes are associated with CD and are present in ≥90% of patients with CD.
Specific HLA serotypes are well documented to be associated with autoimmune enteropathies, specifically celiac disease. HLA-DQ2, and to a lesser extent HLA-DQ8, are found in an extremely large number of patients with celiac disease[1-3]. The structural basis for this finding is that these two MHC class II serotypes bind to the gluten protein gliadin with extremely high affinity, and are subsequently potent activators of anti-gliadin T cells[2,4-6]. In genetically predisposed individuals, this results in an exaggerated immune response that causes intestinal damage, epithelial atrophy, and significant malabsorption. As long as gluten remains in the diet, a similar cycle of intestinal barrier loss, further inflammation and then progressive epithelial damage results. Of note, most individuals that possess HLA-DQ2 or HLA-DQ8 will never develop celiac disease[7], but the high presence of these two serotypes in individuals with the disease suggests that under pro-inflammatory conditions, these individuals may be highly susceptible to intestinal barrier loss and development of the condition. Additionally, HLA-DQ2 and DQ8 may be associated with the development of other autoimmune diseases, such as type 1 diabetes and

Hashimoto's thyroiditis[8,9], suggesting that their association with T cell autoreactivity is likely not limited to a gluten-mediated process.

Given the known inflammatory milieu in the post-transplant setting and the ubiquity of gluten in the North American diet, we initially hypothesized HLA-DQ alleles associated with CD risk would confer increased risks of acute (a) and chronic (c) GVHD in pediatric SCT recipients.

We performed a retrospective cohort study of children aged 0-21 years undergoing first allogeneic SCT at the Children's Hospital of Philadelphia from 10/1/12 — 7/1/16. Patients with primary graft failure or missing HLA-DQ genotypes were excluded. We grouped patients by low, moderate or high CD risk using a published approach.[10] Primary outcomes were 1) 100-day aGVHD incidence; 2) day 100 — 1-year cGVHD incidence; and 3) time to GVHD with relapse, death, secondary graft failure, second SCT, or donor lymphocyte infusion as competing risks. Logistic regressions were used to calculate odds ratios (OR) and 95% confidence intervals (CI). Sub-distribution hazard models were used to estimate crude and adjusted sub-distribution hazard ratios (sHR) in time-to-event analyses. Multivariate models were adjusted for race-ethnicity, malignant/nonmalignant SCT indication, donor/mismatch, and graft source.

We identified 167 patients (mean age 9.2 ±6.2 years; **Table 1**). Proportions by CD risk were: low-risk n=108 (64.7%), moderate n=33 (19.8%), and high n=26 (15.6%). Day 100 incidence of ≥grade 2 aGVHD was 14.4% (8.4% had ≥grade 3). cGVHD 1-year incidence was 42.7% (14% had extensive). Strikingly, CD risk was ***protective*** against GVHD but did not reach statistical significance in simple proportions (**Table2**). Risk of clinically significant GVHD (≥grade 2 or any chronic) was reduced in children with CD risk in the adjusted time-to-event model (moderate: sHR 0.42, 95% CI 0.18 — 0.95, p=0.037; high: sHR 0.31, 95% CI 0.12 – 0.8, p=0.016; **Figure 1A**). The protective effect of high CD risk was more pronounced for severe GVHD (≥grade 3 or chronic extensive) and approached but did not reach statistical significance (adjusted sHR 0.14, 95%CI 0.02-1.09, *P* = 0.061; **Figure 1B**).

In contrast to our initial hypothesis, **CD risk by HLA-DQ is protective against GVHD in a dose-responsive manner.** Reports of HLA-DQ2 and DQ8 protecting against other non-CD autoimmune diseases, specifically IBD, support our observations.[11-13]

Table 1: Patient characteristics – overall and by exposure

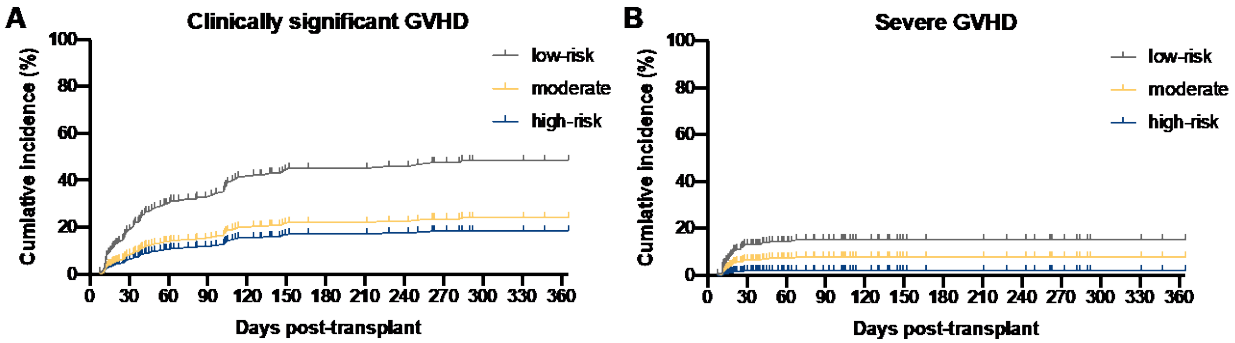
Characteristic	Overall population (N= 167)	Strong celiac risk (n= 26)	Moderate celiac risk (n= 33)	Low celiac risk (n= 108)	*P**
Age, mean ± SD	9.2 ± 6.2	9.7 ± 6.2	7.2 ± .9	9.4 ± 6.3	
Sex, n (%)					
male	97 (58.1)	15 (15.5)	21 (21.6)	61 (62.9)	0.7659
female	70 (41.9)	11 (15.7)	12 (17.2)	47 (67.1)	
Race-ethnicity, n (%)					
White, non-Hispanic	87 (52.1)	16 (18.4)	19 (21.8)	52 (59.8)	0.5690
Black, non-Hispanic	22 (13.2)	1 (4.5)	4 (18.2)	17 (77.3)	
Hispanic	26 (15.6)	3 (11.5)	6 (23.1)	17 (65.4)	
Other/unknown	32 (19.1)	6 (18.8)	4 (12.5)	22 (68.7)	
Diagnosis, n (%)					
Malignant	88 (52.7)	19 (21.6)	21 (23.9)	48 (54.6)	0.0119
Non-Malignant	79 (47.3)	7 (8.8)	12 (15.2)	60 (76.0)	
Donor Type, n (%)					
Matched related donor	53 (31.7)	11 (20.8)	4 (7.5)	38 (71.7)	0.1318
Matched unrelated donor	80 (47.9)	9 (11.2)	22 (27.5)	49 (61.3)	

Mismatched unrelated donor	19 (11.4)	4 (21.0)	3 (15.8)	12 (63.2)	
Mismatched related donor	15 (9.0)	2 (13.3)	4 (26.7)	9 (60.0)	
Graft Source, n (%)					
Peripheral Blood Stem Cell	75 (44.9)	10 (13.3)	19 (25.3)	46 (61.4)	0.1966
Bone Marrow	79 (47.3)	13 (16.5)	10 (12.7)	56 (70.9)	
Cord Blood	13 (7.8)	3 (23.1)	4 (30.8)	6 (46.1)	
T- Cell Depletion, n (%)					
CD3 depletion, no add back	10 (6.0)	2 (20.0)	2 (20.0)	6 (60.0)	0.1798
CD3 depletion, with add back	24 (14.5)	5 (20.8)	3 (12.5)	16 (66.7)	
Alpha/Beta T cell depletion	38 (22.9)	2 (5.3)	13 (34.2)	23 (60.5)	
No T cell depletion	94 (56.6)	16 (17.0)	15 (16.0)	63 (67.0)	
Conditioning Regimen, n (%)					
TBI	68 (40.7)	16 (23.5)	16 (23.5)	36 (53.0)	0.0189
Busulfan	67 (40.1)	7 (10.4)	15 (22.4)	45 (67.2)	
Neither	32 (19.2)	3 (9.4)	2 (6.2)	27 (84.4)	
Serotherapy, n (%)					
ATG	76 (45.5)	6 (8.3)	18 (23.7)	53 (68.4)	0.0006
Campath	24 (14.4)	2 (8.3)	0 (0)	22 (91.7)	
Neither	67 (40.1)	18 (26.9)	15 (22.4)	34 (50.7)	
GVHD Prophylaxis, n (%)					
Tac/CSA	131 (78.4)	23 (17.5)	20 (15.3)	88 (67.2)	0.0154
MMF	64 (38.3)	9 (14.1)	7 (10.9)	48 (75.0)	0.0510
Methotrexate	12 (7.2)	2 (16.7)	3 (25.0)	7 (58.3)	0.8738
Other	13 (7.8)	4 (30.8)	2 (15.4)	7 (53.8)	0.2888

Table 2: Adjusted comparisons of the occurrence of clinically significant GVHD by CD risk

	OR (95% CI)	***P***
aGVHD		
moderate	0.60 (0.16 — 2.25)	0.45
high	0.13 (0.01 — 1.28)	0.08
cGVHD		
moderate	0.44 (0.17 — 1.13)	0.09
high	0.30 (0.09 — 1.00)	0.05

Figure 1: Cumulative incidence of GVHD by HLA-DQ-defined celiac disease risk



Clinically significant GVHD: grade ≥2 acute OR any chronic GVHD; severe GVHD: grade ≥3 acute OR chronic extensive GVHD.
Relapse, death, secondary graft failure, second transplant, or donor lymphocyte infusion were treated as competing risks.
Models adjusted for race-ethnicity, malignant/non-malignant SCT indication, donor/mismatch (matched related, matched unrelated, mismatched unrelated, or mismatched related), and graft source.

Patient eligibility population:
All patients aged 0-21 years undergoing first allogeneic transplantation with available HLA-DQB1 typing from 1/1/2013 – 12/31/2019

Data requirements:
Demographics:

- Date of birth
- Sex
- Race
- Ethnicity

Baseline factors:

- Date of transplant
- prior auto SCT (#) and dates
- multiple donors y/n
- donor type
- product type
- graft manipulation
- baseline Karnofsky/Lansky
- h/o prior inflammatory bowel disease diagnosis
- preparative regimen (categorization and individual conditioning agents)
- GVHD prophylaxis
- post-transplant disease-directed therapy
- Complete HLA typing data (patient and donor)
- transplant indication
- disease status at transplantation including MRD (if applicable)
- leukemia predisposition syndrome

Post-transplant factors:

- date of engraftment (ANC, platelets)
- date of acute GVHD onset
- maximum stage by organ and maximum grade of acute GVHD

- date of chronic GVHD onset
- maximum chronic GVHD grade
- limited or extensive chronic GVHD
- date off immunosuppression
- date of relapse
- date of secondary graft failure
- date of second transplant
- date of first donor lymphocyte infusion
- date of cytotoxic T lymphocyte or other cellular therapy infusion
- date of death

Sample requirements:
N/A

Study design:
This will be a retrospective cohort study of children aged 0-21 years undergoing first allogeneic SCT for any indication from 1/1/2013 — 12/31/2019. Patients with missing HLA-DQ genotypes will be excluded.
Exposure: We will group patients by low, moderate or high CD risk as determined by HLA-DQA1 and DQB1.[10]

Outcomes:
Primary outcomes:
- 1-year incidence of any acute GVHD by HLA DQ status
    - Clinically significant (grade II-IV acute)
    - Severe (grade III-IV acute)
- 1-year incidence of any chronic GVHD by HLA DQ status
    - Clinically significant (limited or extensive chronic)
    - Severe (extensive chronic)
- Incidence of gut GVHD by HLA DQ status
    - Clinically significant (stage II-IV acute)
    - Severe (stage III-IV acute)
    - Incidence by site of disease (upper and lower GI tract) – descriptive only
- Overall survival – 1-year, 5-year (censor at last f/u) by HLA DQ status
- Event-free survival – 1-year, 5-year (censor at last f/u) by HLA DQ status
    - Event = first of graft failure, relapse, second transplant, donor lymphocyte infusion, death
- non-relapse/transplant-associated mortality – 1- year (relapse is a competing risk) by HLA DQ status
- Leukemia stratum only:
    - GVHD/relapse-free survival – 1-year, 5-year (censor at last f/u) by HLA DQ status
    - Time to relapse – 1-year, 5-year (censor at last f/u) by HLA DQ status

Secondary outcomes:
- Time to GVHD onset with relapse, death, or secondary graft failure, receipt of viral CTLs, 2nd transplant, or DLI as competing risks
    - Clinically significant (grade II-IV acute OR limited or extensive chronic)
    - Severe (grade III-IV acute OR extensive chronic)
- 1-year incidence of secondary graft failure (relapse and death as competing risks) by HLA DQ status
- 30-day incidence of primary graft failure by HLA-DQ (with death as a competing risk)

- Time to cessation of immunosuppression by HLA DQ risk

Statistical analyses:
Log-binomial regressions will be used to calculate risk ratios and 95% confidence intervals. Sub-distribution hazard models will be used to estimate crude and adjusted sub-distribution hazard ratios in time-to-event analyses. We will evaluate univariate associations and perform a stepwise approach to select covariates for inclusion into multivariate models.
In order to reduce analytic burden for the CIBMTR on this retrospective cohort analysis, we would be able to perform these analyses locally if provided with a raw dataset.

Non-CIBMTR data source:
N/A

Conflicts of interest:
None

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Characteristics of pediatric patients undergoing first alloHCT from 2008-2018 with DQB1 HLA data available, as reported to the CIBMTR

Characteristic	Positive*	Negative
No. of patients	1455	2670
No. of centers	136	162
Transplant performed in US?		
Yes	1029 (71)	2094 (78)
No	426 (29)	576 (22)
HLA-DQB1 typing		
Two of specified types	172 (12)	0
DQB1*0302	493 (34)	0
DQB1*0201	405 (28)	0
DQB1*0202	385 (26)	0
Other	0	2670
HLA-DQA1 typing available		
Yes	58 (4)	239 (9)
No	1397 (96)	2431 (91)
Age at HCT		
Median (min-max)	7 (0-20)	7 (0-20)
<10	901 (62)	1567 (59)
10-17	421 (29)	822 (31)
18-21	133 (9)	281 (11)
Gender		
Male	867 (60)	1603 (60)
Female	588 (40)	1067 (40)
Disease		
AML	287 (20)	500 (19)
ALL	282 (19)	503 (19)
CML	15 (1)	28 (1)
MDS	70 (5)	150 (6)
Other acute leukemia	0	1 (0)
Other leukemia	21 (1)	35 (1)
NHL	36 (2)	53 (2)
HD	6 (0)	28 (1)
Other malignancies	1 (0)	6 (0)
Severe aplastic anemia	119 (8)	254 (10)
Inherited abnormlaities erythrocyte differentiation or function	216 (15)	491 (18)
SCID and other immune system disorders	210 (14)	359 (13)
Inherited abnormlaities of platelets	5 (0)	16 (1)
Inherited disorders of metabolism	117 (8)	142 (5)
Histiocytic disorders	63 (4)	92 (3)

Characteristic	Positive*	Negative
Autoimmune diseases	5 (0)	3 (0)
Other	2 (0)	9 (0)
Donor type		
HLA-identical sibling	222 (15)	547 (20)
Other related	294 (20)	542 (20)
Well-matched unrelated (8/8)	270 (19)	532 (20)
Cord blood	669 (46)	1049 (39)
Conditioning regimen intensity		
MAC	1041 (72)	1836 (69)
RIC	149 (10)	336 (13)
NMA	158 (11)	321 (12)
TBD	61 (4)	113 (4)
Missing	46 (3)	64 (2)
GVHD prophylaxis		
Ex-vivo T-cell depletion	42 (3)	78 (3)
CD34 selection	54 (4)	76 (3)
Post-CY + other(s)	137 (9)	270 (10)
Post-CY alone	1 (0)	1 (0)
TAC + MMF ± other(s) (except post-CY)	152 (10)	345 (13)
TAC + MTX ± other(s) (except MMF, post-CY)	175 (12)	375 (14)
TAC + other(s) (except MMF, MTX, post-CY)	49 (3)	66 (2)
TAC alone	9 (1)	29 (1)
CSA + MMF ± other(s) (except post-CY)	339 (23)	621 (23)
CSA + MTX ± other(s) (except MMF, post-CY)	208 (14)	399 (15)
CSA + other(s) (except MMF, MTX, post-CY)	164 (11)	189 (7)
CSA alone	31 (2)	55 (2)
Other(s)	18 (1)	34 (1)
Missing	76 (5)	132 (5)
Year of transplant		
2008	262 (18)	364 (14)
2009	162 (11)	264 (10)
2010	91 (6)	250 (9)
2011	59 (4)	162 (6)
2012	102 (7)	198 (7)
2013	115 (8)	219 (8)
2014	96 (7)	244 (9)
2015	107 (7)	230 (9)
2016	114 (8)	209 (8)
2017	186 (13)	276 (10)
2018	161 (11)	254 (10)

Characteristic	Positive*	Negative
Follow-up of survivors, months - median (min-max)	51 (1-129)	53 (1-133)

* HLA-DQB1 typing of at least one of the following: *0302, *0201, *0202

Proposal: 1911-81

Title:
Investigate the association of HLA-A*0101 allele expression and risk for acute cutaneous GVHD

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Research hypothesis:
HLA-A*0101 expression is associated with increased risk of severe acute cutaneous GVHD at day 180.

Specific aims:
- To investigate whether HLA-A*0101 expression is associated with increased risk of grade II-IV and III-IV cutaneous aGVHD after allogeneic hematopoietic stem cell transplantation (alloHSCT).
- To assess if HLA-A*0101 expression in patients has an impact on transplant-related mortality (TRM) and overall survival (OS) after alloHSCT.
- To determine the effect of T-cell depletion (TCD) vs. unmodified alloHSCT on associations between HLA-A*0101 expression and cutaneous aGVHD, TRM, OS.
- To determine association between CMV, HHV6, Adenovirus, and EBV viremia and cutaneous aGVHD onset in patients with and without HLA-A*0101.

Scientific impact:
Acute graft-versus-host disease (aGVHD) after alloHSCT remains a significant cause of morbidity and non-relapse mortality in hematologic cancer survivors. Several risk factors for the development of aGVHD have been identified including degree of HLA disparity between donor and recipient, intensity of conditioning regimen, choice of GVHD prophylactic regimen and the source of the allograft among others[1].These have led to the implementation of varied therapeutic strategies to decrease GVHD risk, such as the use of *ex vivo* CD34+ selected/T-cell depleted (TCD) allografts[2]. However, even after TCD alloHSCT, cumulative incidences of grade I-IV aGVHD still reach 23% at day 180 after transplant [2].
The skin is the organ most commonly affected by aGVHD and is often the first clinical manifestation of the disease. Cutaneous aGVHD typically demonstrates a high response to therapy after both unmodified and TCD transplants[3]. However, we identified a cluster of patients who experienced severe refractory cutaneous acute and late aGVHD after TCD and unmodified alloHSCT and expressed MHC class I HLA-A*0101. Development of severe aGVHD, despite treatment with high-dose corticosteroids, is associated with an increased risk of non-relapse mortality[4].
These findings would have practical implications for allogeneic transplant recipients, both in the development of prophylactic therapies to reduce their risk for cutaneous aGVHD, and of early therapeutic strategies targeting the skin in this high-risk HLA-A*01:01 population.

Scientific justification:
The pivotal initial event in the development of GVHD is the recognition of antigens on host cells by donor-infused immune cells. Among patients who receive grafts from HLA-identical siblings, GVHD may develop due to differences in minor histocompatibility antigens (MiHA), which are inherited independently of HLA, but are HLA restricted. Incidence of GVHD may vary according to HLA type because HLA molecules differ in their ability to present relevant MiHA to the incoming donor-derived T cells[5]. HLA-B18 was associated with a threefold increased risk of grade I-IV aGVHD[6], while HLA-B8 was associated with nearly half the relative risk of aGVHD. The high incidence of aGVHD in patients with HLA-

B18 may be due to a stronger than normal immune response or of a deficit in T cells otherwise suppressing the response to non-HLA antigens of the recipients[6]. HLA-B44, HLA-A26, HLA-A3 were associated with increased risk for aGVHD, while HLA-B7, DR3 was protective[7,8]. Differences in aGVHD risk associated with HLA-B7 and B44 were attributed to the ability to present particular minor histocompatibility (MHC) antigens or viral antigens which are responsible for aGVHD in MHC matched grafts or due to an antigen non-specific gene influence within the MHC on the development of aGVHD[8]. Furthermore, HLA-A*01 prohibits efficient immune responses leading to genetic variation in T-cell responses, influencing the nature of primary EBV infection as well as the level of viral persistence[12, 13]. This may be due to HLA-A*01 inability to present highly immunogenic peptides of EBV-derived peptides or only present EBV-derived peptides of low immunogenicity[12]. Consequently, HLA-A*01 individuals may not be able to evoke an efficient cytotoxic T-lympocyte (CTL) response[12]. Alternatively, HLA-A*01 alleles may be predisposed to increased frequency of nonneoplastic EBV-infected B cells due to impaired immune surveillance[12].

A single center analysis was conducted. We evaluated alloHSCT recipients (n = 831) from 03/2010 to 02/2017 who received either an unmodified or an *ex vivo* CD34+ selected allograft. Because all patients had 8/8 HLA-allele matched donors, both donor and recipient either expressed HLA-A*0101 or did not. HLA-A*0101 was expressed in 206 (25%) patients (98 TCD, 108 unmodified) who had similar demographics to patients lacking HLA-A*0101.

Donor-recipient expression of HLA-A*0101 correlated with an increased incidence and severity of cutaneous aGVHD. At day 180, patients expressing HLA-A*0101 had a higher incidence of grade III-IV cutaneous aGVHD compared with patients lacking HLA-A*0101 expression in both the $CD34^{+}$-selected (8% vs. 3%, p=0.027) and unmodified (11% vs. 4%, p=0.01) cohorts. In a multivariate analysis the presence of HLA-A*0101 correlated with increased risk of grade III-IV cutaneous aGVHD in CD34+ selected and unmodified graft recipients.

We seek to validate our institutional findings in the larger CIBMTR database. This project aims to improve alloHSCT recipient by identifying patients at risk for severe refractory cutaneous aGVHD earlier and developing proactive methods based on HLA-A*0101 expression.

Patient eligibility population:

- History of primary allogeneic HSCT for treatment of acute leukemia or MDS between 2014-2018
- Exclude recipients of <8/8 HLA-matched grafts, cord blood transplantations, or >1 alloHSCT

Data requirements:

- Form 2400 R5.0 Pre-Transplant Essential Data: Recipient Data, HCT; Donor Information; Product processing/Manipulation, Clinical Status of Recipient Prior to the Preparative Regimen; Comorbid Conditions; Pre-HCT Preparative Regimen; GVHD Prophylaxis
- Form 2006 R4.0 Hematopoietic Cellular Transplant (HCT) Infusion: Product Analysis
- Form 2005 R6.0 Confirmation fo HLA Typing: HLA Typing by DNA Technology for recipient and donor
- Form 2402 R3.0 Disease Classification: Primary Disease for HCT/Cellular Therapy; AML; ALL; Acute Leukemias of Ambiguous Lineage and Other Myeloid Neoplasms; MDS/MPN; Status at transplantation
- Form 2450 R4.0 Post-Transplant Essential Data and Form 2100 R5.0 Post-HCT Follow-up Data: Survival; Subsequent Transplant; Initial ANC Recovery; Initial Platelet Recovery; Graft vs Host Disease; New Malignancy, Lymphoproliferative or Myeloproliferative Disease/Disorder; Relapse or Progression Post-HCT; Current Disease Status; Immune Reconstitution; Chimerism studies
- Form 2150 R1.0 CMV/EBV/ADV/HHV-6/BK Viral Infection Diagnostic and Treatment: Infection Episode; PCR Tissue Sample

Table 1 Data Requirements:

Type	Data point	Specific data
Patient Specific	Patient specific characteristics (Forms 2400 R5.0; 2402 R3.0)	• Age at transplant (Date of birth); Gender; Race/Ethnicity • Significant comorbidities/Performance Status; Weight • Primary disease type (AML, ALL, MDS); Disease risk (high risk or standard); Remission status (CR1, CR2, etc) • Prior autologous transplant
Transplant Specific	Transplant information (Form 2400 R5.0)	• Transplant date • Peripheral blood stem cell or Bone Marrow • Donor type, donor age
	Preparative regimen (Form 2400 R5.0)	• Myeloablative; Reduced Intensity/ non-myeloablative • TBI
	GVHD prophylaxis (Form 2400 R5.0)	• Calcineurin inhibitor based (cyclosporin, tacrolimus); Sirolimus; Corticosteroids; Other • T-Cell Depletion and method • ATG (rabbit, equine or none)
	Graft characteristic (Forms 2005 R6.0; 2006 R4.0)	• Donor-recipient HLA match • Donor-recipient class I allele match if available • Infused TNC cell dose • Infused CD34+ cell dose • Infused CD3+ cell dose
	Engraftment (Forms 2450 R4.0; 2100 R5.0)	• Time to absolute neutrophil count $\geq$500 cells/mm^3 • Time to unsupported platelets $\geq$20 x 10^9 cells/L and $\geq$50 x 10^9 cells/L • Donor-recipient chimerism • Graft failure (primary and secondary)
Outcome Measures	GVHD (Form 2450 R4.0; 2100 R5.0)	• Acute GVHD (aGVHD): Incidence of grade II-IV acute GVHD (aGVHD) (subset evaluating grade III-IV aGVHD); and by organ stage; onset • GVHD after day 100: Incidence of chronic GVHD (cGVHD) • Severity of GVHD after day 100
	Mortality (Form 2450 R4.0; 2100 R5.0)	• Time to mortality; Day 100, 6-month and 1-year mortality • Treatment related mortality at 6 months and 1 year: Cause of death
	Disease relapse (Form 2450 R4.0; 2100 R5.0)	• Incidence of disease relapse; Time to disease relapse
	Immune reconstitution (Form 2450 R4.0; 2100 R5.0)	• Incidence of EBV PTLD; Recovery of ALC, CD3+4+, CD3+8+ T lymphocytes
	Viremia (Form 2150 R1.0)	• Infectious serologies/PCRs (CMV, EBV, ADV, HHV6) and onset date

Sample requirements:
N/A

Study design:
This will be a retrospective cohort study examining outcomes among age-matched, disease-matched patients with HLA-A*0101 expression compared to those without. Patients in the CIBMTR registry with history of allogeneic HSCT for treatment of acute leukemia or MDS between 2014-2018 will be included (patients with cord blood source or <8/8 HLA donor-recipient match will be excluded). Patients will be stratified into the study according to HLA-A*0101 expression vs. no expression.

Primary outcomes:
will be incidence and severity of cutaneous acute and late acute GVHD at day 180 between alloHSCT patients with HLA-A*0101 expression and those without. *We hypothesize that it would be feasible to apply multivariate statistical methods within a multi-institutional database to confirm the association of HLA-A*0101 expression and risk of severe cutaneous aGVHD noted within our institution.*

Secondary outcomes:
- Differences in transplant-related mortality (TRM) and overall survival (OS) after alloHSCT between cutaneous aGVHD patients with HLA-A*0101 expression and those without.
- *We will apply multivariate statistical methods within the CIBMTR database to determine the association of HLA-A*0101 expression and TRM and OS.*
- To determine the effect of T-cell depletion (TCD) vs. unmodified alloHSCT on associations between HLA-A*0101 expression and cutaneous aGVHD, TRM, OS.
- *We will apply multivariate statistical methods within the CIBMTR database to determine the association of HLA-A*0101 expression and T-cell depletion in aGVHD, TRM, and OS.*
- Incidence of cutaneous aGVHD in patients with HLA-A*0101 with viremia preceding rash versus those without preceding viremia as well as incidence of cutaneous aGVHD in patients without HLA-A*0101 with viremia preceding rash versus those without preceding viremia.
- *We will apply multivariate statistical methods within the CIBMTR database to determine the association of preceding (CMV, EBV, ADV, HHV-6) viremia and cutaneous aGVHD among patients with and without HLA-A*0101.*

Non-CIBMTR data source:
N/A

Conflicts of interest:
No

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Characteristics of adult patients undergoing first alloHCT from HLA-identical sibling or 8/8-matched unrelated donor from 2014-2018, as reported to the CIBMTR

Characteristic	HLA-A*01 Positive	HLA-A*01 Negative
No. of patients	690	2199
No. of centers	120	155
No. of centers	16	20
Transplant performed in US?		
Yes	640 (93)	2085 (95)
No	50 (7)	114 (5)
Age at HCT		
Median (min-max)	63 (18-81)	61 (18-82)
18-29	33 (5)	114 (5)
30-39	24 (3)	100 (5)
40-49	54 (8)	215 (10)
50-59	148 (21)	507 (23)
60-69	316 (46)	985 (45)
≥70	115 (17)	278 (13)
Gender		
Male	403 (58)	1300 (59)
Female	287 (42)	899 (41)
Disease		
AML	248 (36)	841 (38)
ALL	70 (10)	230 (10)
MDS	372 (54)	1128 (51)
Graft type		
Bone marrow	92 (13)	260 (12)
Peripheral blood	598 (87)	1939 (88)
Conditioning regimen intensity		
MAC	291 (42)	1002 (46)
RIC	334 (48)	1019 (46)
NMA	28 (4)	86 (4)
TBD	20 (3)	50 (2)
Missing	17 (2)	42 (2)
GVHD prophylaxis		
Ex-vivo T-cell depletion	0	11 (1)
CD34 selection	6 (1)	34 (2)
Post-CY + other(s)	31 (4)	94 (4)
Post-CY alone	3 (0)	20 (1)
TAC + MMF ± other(s) (except post-CY)	120 (17)	360 (16)
TAC + MTX ± other(s) (except MMF, post-CY)	367 (53)	1130 (51)

Characteristic	HLA-A*01 Positive	HLA-A*01 Negative
TAC + other(s) (except MMF, MTX, post-CY)	43 (6)	157 (7)
TAC alone	9 (1)	40 (2)
CSA + MMF ± other(s) (except post-CY)	28 (4)	111 (5)
CSA + MTX ± other(s) (except MMF, post-CY)	44 (6)	130 (6)
CSA + other(s) (except MMF, MTX, post-CY)	1 (0)	5 (0)
CSA alone	2 (0)	6 (0)
Other(s)	10 (1)	23 (1)
Missing	26 (4)	78 (4)
Year of transplant		
2014	163 (24)	598 (27)
2015	153 (22)	460 (21)
2016	106 (15)	333 (15)
2017	154 (22)	455 (21)
2018	114 (17)	353 (16)
Cutaneous aGVHD?		
Yes		
Stage 1	47 (7)	139 (6)
Stage 2	41 (6)	157 (7)
Stage 3	96 (14)	273 (12)
Stage 4	18 (3)	47 (2)
No	488 (71)	1583 (72)
Follow-up of survivors, months - median (min-max)	38 (2-62)	36 (3-65)

Proposal: 1911-252

Title:
Prediction of Graft-Versus-Host Disease in Recipients of Hematopoietic Cell Transplant from a Single Mismatched Unrelated Donor Using a Highly-Multiplexed Proteomics Assay: MHC-PepSeq

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Research hypothesis:
We have developed a novel assay (MHC-PepSeq) to identify non-self-peptides in HLA mismatch donor/recipient pairs. Non-self-peptides will be derived from the mismatched recipient HLA I/II proteins, which can be bound and presented by class II HLA molecules, following which they can be targeted by the donor T cells. In this proposal, *we hypothesize that the risk score derived from the MHC-PepSeq assay is associated with the incidence and severity of acute and chronic graft-versus-host disease (GVHD)*.

Specific aims:
Aim 1:
Evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in recipients of allogeneic hematopoietic cell transplantation (HCT) from a 8/8 matched donor with a mismatch in HLA-DP.

Aim 2:
Evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in HCT recipients from a 7/8 HLA mismatched donor.

Scientific impact:
Allogeneic HCT is the most effective treatment for patients with hematologic malignancies or inherited blood disorders. However, genetic mismatches in protein coding genes between the donor and recipient can elicit an alloimmunity response, leading to serious complications such as graft rejection and GVHD. While high-resolution HLA genotyping is routinely performed for identifying matched donors for recipients of allogenic HCT, finding a perfect match is not possible for majority of HCT recipients. Therefore, the transplant team is frequently faced with the dilemma of selecting a donor from multiple potential variably mismatched donors, based on whether the benefits of the transplant from each donor outweigh its risks.
The key accomplishment of this project, if successful, is an algorithm that takes HLA genotypes from donor and recipient and outputs a GvHD risk score. This algorithm requires no other input apart from the HLA genotype information that transplant clinicians routinely generate. Therefore, it would be immediately available to help guide decision-making in donor selection process, upon dissemination. The unmet need for such a tool is evidenced by the many attempts in the field to generate matching algorithms, none of which has fulfilled the unmet need.

Scientific justification:
GVHD remains a major cause of mortality and morbidities after allogeneic HCT. GVHD involves immunological attack of recipient tissues – typically the skin, gut and/or lungs – by donor-derived T cells existing in the graft.[1] Currently, the major predictor of GVHD occurrence after allogeneic HCT is the level

of HLA allele mismatched/matched between the donor and the recipient.[2] As a result, large registries of HLA-genotyped prospective donors such as the National Marrow Donor Program (NMDP) have been assembled. Despite these resources, and the availability of matched related donors for some patients, the majority of transplants are mismatched in at least 1 HLA loci,[3] and identifying the best matched donor based on the benefits of a transplant versus its risks, remains a dilemma for transplant clinicians.

Existing approaches to HLA matching:

The morbidity and mortality associated with GVHD and graft rejection, together with the increasingly-routine use of high-resolution HLA genotyping, has generated considerable interest in the possibility of identifying permissive and non-permissive HLA mismatches that can be used to guide decision making in transplantation. Currently available methods include: (i) the prediction of anti-HLA alloantibody recognition based on the 3D structure of HLA (*HLAmatchmaker*), (ii) examination of the direct recognition profiles of patient-derived HLA-DP-reactive T cell clones (*DP direct epitopes*), and (iii) the enumeration of indirectly-presented peptides identified by an *in silico* HLA binding algorithm (*PIRCHE*).

'Indirect recognition' as a key molecular pathway of alloimmunity:

T cells recognize antigens in the form of a peptide. HLA complex are displayed on the surface of antigen-presenting cells and Self T cells are actively tolerized to the 'self' antigen complexes that were encountered to them during development. While this system normally enables remarkably specific immunity against foreign pathogens while sparing self-tissues, it carries the risk of a T cell-mediated pathology ('alloimmunity') when T cells encounter genetically-distinct tissue following allogeneic transplantation. Indirect recognition is a major molecular pathway leading to alloimmunity, which occurs when T cells respond to *non-self*-peptides ('allopeptides') presented by *self* HLA proteins.[4] Allopeptides can exist across the genome, but are frequently derived from the HLA protein itself, since it is a protein family that is both highly-expressed and highly-polymorphic. *It is important to note that HLA serves two distinct roles in this model: (1) non-self HLA serves as the source of the antigenic peptides, and (2) self-HLA serves as the presenting proteins by which such peptides are bound and made visible to T cells.*

As illustrated in **Figure 1,** in the setting of HCT, indirect presentation of allopeptides derived from recipient / non-self HLA class I or II proteins (expressed by non-hematopoietic tissues) by donor / self HLA class II proteins (on donor antigen presenting cells) is the major driver of GVHD.[5,6] A broadly analogous process leads to tissue rejection in the case of solid organ transplantation.[7,8]

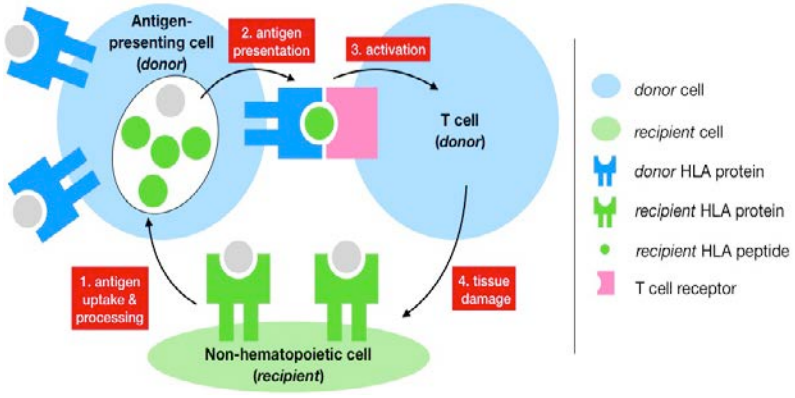

Figure 1. 'Indirect recognition' of mismatched HLA as a driver of GVHD in HCT. Mature T cells in a graft express T cell receptors that are not tolerant to recipient-derived peptides. 'Indirect recognition' occurs when polymorphic proteins expressed by non-hematopoietic cells of the recipient – including the HLA itself (green) – are taken up by donor antigen-presenting cells and processed into peptides for display as peptide:HLA complexes. Although these complexes contain self HLA (blue), the non-self-peptide (green) can be recognized by donor T cells, leading to tissue damage.

MHC-PepSeq: A novel and highly-parallel approach to allopeptide identification:

Although the contribution of individual HLA-derived allopeptides to disease is well-established in both

solid organ and HCT settings, there has been little attempt to define these peptides systemically as a basis for predicting clinical outcome. In large part, this reflects the difficulty in ascertaining which peptides, among the many possibilities, can be efficiently presented by which HLA class II molecules. In this project, we aim to address this question using a novel, highly-multiplexed peptide-MHC binding assay, namely "MHC-PepSeq".

The 'PepSeq' platform, initially developed at Prognosys Biosciences and available by license to TGen, enables large and fully-definable libraries of peptides to be synthesized cost-effectively in one-pot reactions and then assayed in multiplex against immunological targets. Library generation takes advantage of *in vitro* transcription and translation of DNA templates, following by intra-molecular coupling to produce biologically-synthesized peptides individually covalently coupled to DNA tags for read out by sequencing. In the 'MHC-PepSeq' assay, a library comprising overlapping 15mer peptides that tile proteins of interest is assayed for binding against a panel of recombinantly-expressed HLA class II molecules, revealing distinct clusters of overlapping peptide binders that represent HLA-restricted epitopes (**Figure 2a**). *In preliminary data, we have demonstrated the capacity of this system to produce and assay the MHC binding of 1000s of pre-programmed 15-mer peptides in parallel*, and shown that the

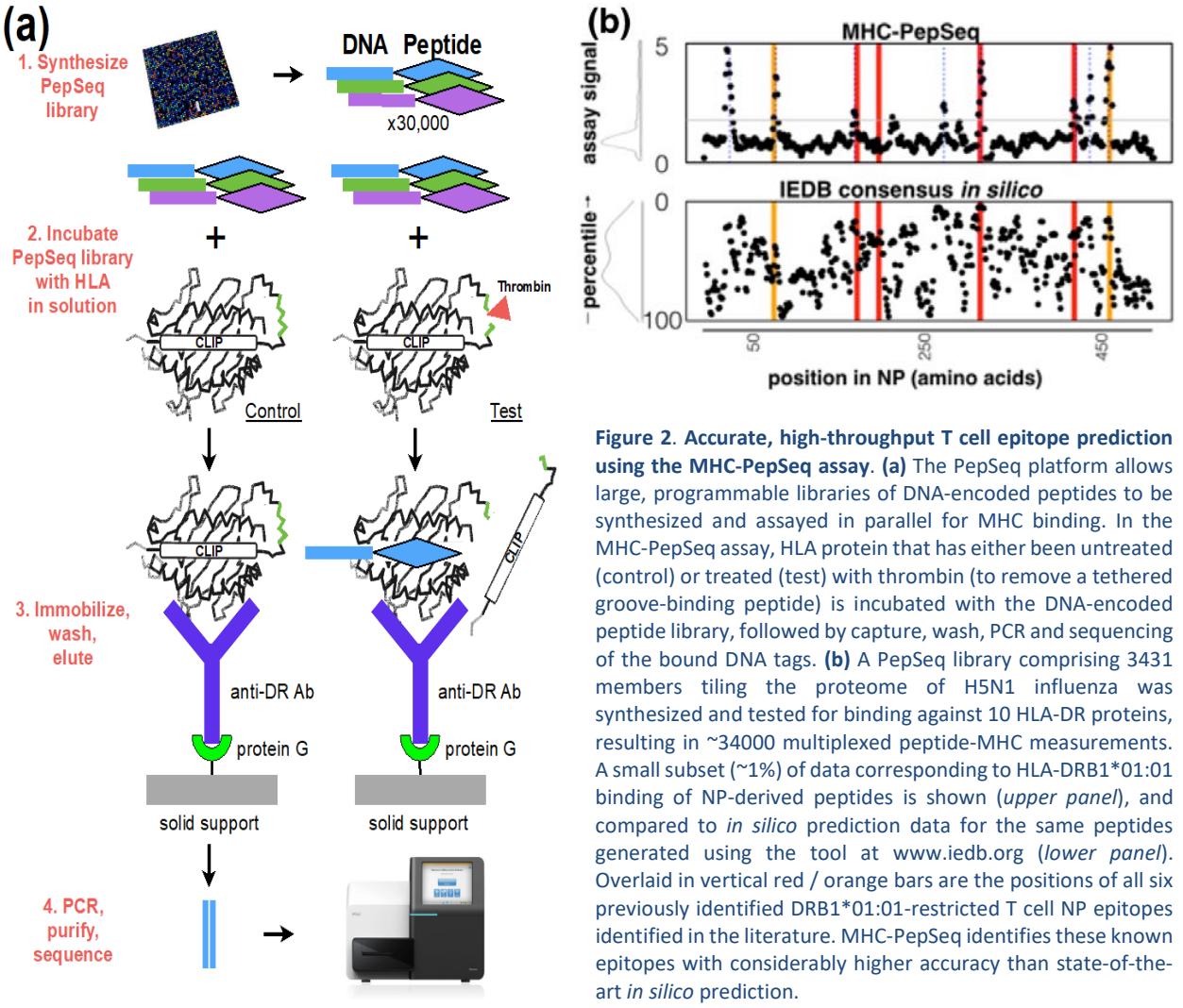

Figure 2. Accurate, high-throughput T cell epitope prediction using the MHC-PepSeq assay. (a) The PepSeq platform allows large, programmable libraries of DNA-encoded peptides to be synthesized and assayed in parallel for MHC binding. In the MHC-PepSeq assay, HLA protein that has either been untreated (control) or treated (test) with thrombin (to remove a tethered groove-binding peptide) is incubated with the DNA-encoded peptide library, followed by capture, wash, PCR and sequencing of the bound DNA tags. **(b)** A PepSeq library comprising 3431 members tiling the proteome of H5N1 influenza was synthesized and tested for binding against 10 HLA-DR proteins, resulting in ~34000 multiplexed peptide-MHC measurements. A small subset (~1%) of data corresponding to HLA-DRB1*01:01 binding of NP-derived peptides is shown (*upper panel*), and compared to *in silico* prediction data for the same peptides generated using the tool at www.iedb.org (*lower panel*). Overlaid in vertical red / orange bars are the positions of all six previously identified DRB1*01:01-restricted T cell NP epitopes identified in the literature. MHC-PepSeq identifies these known epitopes with considerably higher accuracy than state-of-the-art *in silico* prediction.

resulting high-resolution data substantially outperforms existing state-of-the-art *in silico* methods for predicting human T cell responses (**Figure 2b**).

Application of the MHC-PepSeq technology in mismatch donor HCT

In order to test the hypothesis that a comprehensive evaluation of the presentation of HLA-derived allopeptides by HLA class II can predict GVHD and serve as a clinically-valuable approach to donor selection process in allogeneic HCT, we propose to conduct an empirical HLA binding survey of unprecedented scale. Using publicly-available population allele frequency data (http://www.allelefrequencies.net), we have identified a set of class I and II sequences that cover >95% of alleles at each of the major 6 human HLA loci (HLA-A, -B, -C, -DR, -DQ, -DP) in 3 major US populations (European Caucasian, African American, and Mexican Chicano). When represented in the form of densly-overlapping tiled peptides, this set comprises approximately 30,000 unique 15mers, which fits well with the size of 1 PepSeq library. We will encode these peptides in DNA using 3 codings per peptide for a total ~90,000-plex DNA library (*CustomArray*), and use the PepSeq parallel synthesis protocol to generate a library of the corresponding DNA-encoded peptides. This library will then be incubated with recombinantly-expressed full-length HLA proteins, washed, eluted, amplified and sequenced to reveal the various HLA-derived peptides that bind to the assayed HLA proteins.

Full-length, biotinylated HLA class II proteins with tethered CLIP placeholder peptides (as depicted in **Figure 2a**) are available from the Tetramer Core Facility (TCF, http://tetramer.yerkes.emory.edu) under NIH contract. In addition to the reagents that they routinely provide, we have negotiated with TCF to develop an expanded set of 27 HLA-DR proteins that cover ≥90% of each of the 3 populations described above. We are also currently developing a panel of 13 HLA-DQ proteins with similar coverage.

By assaying the 30,000-plex peptide library against the >40 HLA proteins, we will generate >1 million HLA peptide : protein binding measurements. Previous PepSeq data suggests that we will see clusters of signal corresponding to overlapping peptides, each cluster revealing a core binder sequence (typically ~9 amino acids in length). We expect to detect 1 such binder per 100-200 amino acids of sequence space, corresponding to a total of ~8000 binders expected in the experiment. A quantitative estimate for the strength of each binder will also be available, based on the read depth. The redundancy that is built into our approach – using 3 DNA codings per peptide, and tiling proteins with densly overlapping peptides – will enable the binding hits to be identified with high confidence. Accordingly, this stage of the project will have the following outcome: a comprehensive catalog of high-quality HLA-derived binding motifs, which we will make available to the community through the Immune Epitope Database project (http://www.iedb.org).

In summary, We have developed a novel assay (MHC-PepSeq) to identify non-self-peptides in HLA mismatch donor/recipient pairs, derived from the mismatched recipient HLA I/II proteins, which can be bound and presented by class II HLA molecules, and targeted by the donor T cells. A pilot correlative study is currently underway in collaboration between Tgen (John Altin, PhD), Baylor Scott & White Health (Medhat Asker, MD), and City of Hope (Karamjeet Sandhu, MD/Ryotaro Nakamura, MD). The results are expected to be available in the next 2-3 months, which will provide an estimate of the effect size of the prediction model and further inform the design of the proposed large CIBMTR study.

Patient eligibility population:

Inclusion criteria:

- Patient with AML, ALL and MDS who received HCT from an 8/8 matched unrelated donor (Aim 1), or a 7/8 mismatched unrelated donor (Aim 2) based on available high-resolution HLA data
- Disease status for AML/ALL: CR1 or CR2
- Myeloablative or reduced intensity conditioning (truly non-myeloablative regimens such as TBI 200 cGy/fludarabine will be excluded).
- Any GVHD prophylaxis except for ex-vivo T cell depletion and Post-transplant cyclophosphamide (PTCy).
- Bone marrow or peripheral blood stem cells as a graft source.

- Transplant era of 2000-2017 whose acute GVHD data and at least 1-year chronic GVHD data are available.

Data requirements:
Patient-related data will include:
- Age at transplant, Continuous & by age group: decades
- Patient sex: male vs. female
- Karnofsky performance status at transplant: ≥ 90 vs. < 90 vs. missing
- HCT comorbidity index at transplant: 0 vs 1-2 vs ≥ 3 vs. missing

Disease-related data will include:
- Diagnosis, AML, MDS, ALL
- Disease status at transplant

Transplant-related data will include:
- Graft source: peripheral blood vs. bone marrow
- Transplant donor type: 8/8 matched unrelated donor with DP mismatch (HLA-A,B,C,DRB, and 7/8 mismatched unrelated donor
- Donor-recipient gender match: male-male vs. male-female vs. female-male vs. female-female vs. missing
- GVHD prophylaxis: CNI+MTX+others vs. CNI+MMF+others vs. CNI+others vs. vs. others selection vs. others vs. missing
- Time from diagnosis to transplant: continuous
- Donor-recipient CMV status: -/+ vs. others vs. missing
- Year of transplant: continuous
- Conditioning intensity: Myeloablative (MAC) vs. reduced intensity conditioning (RIC)
- ATG use in conditioning: no vs. yes vs. missing

Other data elements (endpoints) include:
- Acute GVHD: yes or no. Time from transplant. Stage/Grade at diagnosis
- Chronic GVHD: yes or no. Time from transplant Stage/Grade at diagnosis
- Time to Neutrophil engraftment
- Time to Platelet engraftment
- Disease relapse: Time to relapse
- Death: Time to death. Cause of death

Sample requirements:
NA

Study design:
MHC PepSeq:
As depicted in **Figure 3,** , we are going to identify the subset of the atlas that is relevant to each donor-recipient pair, using the high-resolution HLA typing data:
- Based on genotypes, we will identify HLA class I and II proteins that are present in the recipient but not the donor, and extract all component 15mer peptide sequences (green fields in Figure 3),

- From the peptide set identified in step #1, we will remove any sequences that are also found in HLA class I or II proteins of the donor – and therefore to which T cells are presumed tolerant (gray fields in Figure 3),
- We will next identify which of the donor HLA class II proteins are present in the HLA protein set (sourced from TCF) (blue fields in Figure 3), and lastly
- We will extract the binding data that intersects the step #2 peptides X step #3 proteins (red fields in Figure 3)

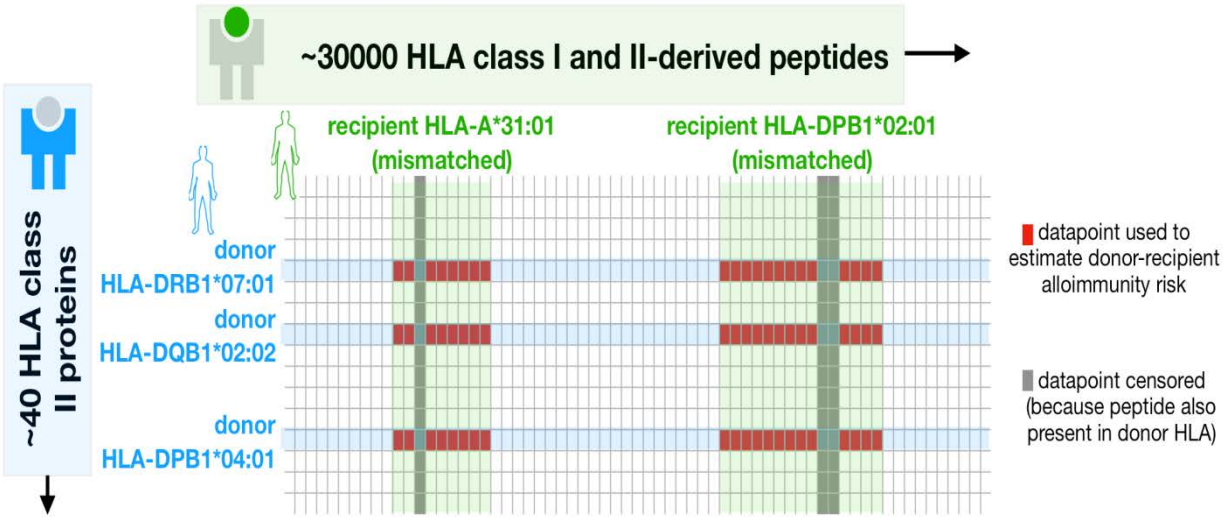

Figure 3. Querying the HLA allopeptide atlas for each given donor-recipient pair. According to the indirect presentation model, the subset of the binding atlas that is relevant to a given transplant corresponds to peptides from mismatched class I / II proteins present in the recipient (among 30,000 total peptides: horizontal axis), binding to class II protein from the donor (among ~40 total proteins: vertical axis). After identifying peptides from mismatched recipient proteins (**green fields**), an important step is to remove those peptides that are nonetheless also present in donor HLA sequences due to homology between alleles (**gray fields**), since there will be immunological tolerance to these. Finally, by considering the class II proteins of the donor (**blue fields**), the binding data relevant to the particular transplant can be identified (**red fields**). This process will be implemented informatically for each donor-recipient pair that is studied.

Using the binding data that is relevant to each donor-recipient pair, we will develop statistical models that consider the number and intensity of donor HLA-binding events as a predictor of the following clinical outcomes: occurrence and intensity of *acute GvHD (primary), chronic GVHD (secondary), and 5-year overall survival, relapse, engraftment,transplant-related mortality (secondary)*. We will conduct the analysis in a step-wise fashion, initially training our models on those cases that are mismatched only at the HLA-DP locus (Aim 1), and then extending the analysis to mismatches at any of the 6 major HLA loci (HLA-A, -B, -C, -DR, -DQ, -DP) (Aim 2).

Analysis plans:

Aim 1:

Evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in recipients of allogeneic hematopoietic cell transplantation (HCT) from a 8/8 matched donor with a mismatch in HLA-DP.

Patients who have undergone HCT from an 8/8 (HLA-A, -B, -C, and -DR) matched unrelated donor by high resolution typing from 2000-2017 will be included in the analyses. These cases will be divided into a training and validation cohort. MHC PepSeq binding data outcome discerning high risk and low risk will be initially applied to the training cohort to further refine the MHC PepSeq algorithm in predicting acute GVHD (grade 2-4 and 3-4). On the development of the MHC PepSeq prediction algorithm will use a

multivariate hazard model adjusting for confounding variables. These variables include, but not limited to: age, conditioning intensity, GVHD prophylaxis, permissive/non-permissive DP mismatch, and high/low HLA-DP expression (rs9277534G vs. rs9277534A).[9] The MHC PepSeq prediction model developed in the training cohort will be tested in the validation cohort.

Aim 2:
Evaluate the performance of the MHC-PepSeq model in predicting acute and chronic GVHD in HCT recipients from a 7/8 HLA mismatched donor.
After completion of the HLA allopeptide atlas for the entire HLA-A, B, C, and DR, we will begin analyses on the 7/8 HCT cohort in a similar fashion. The study will ideally evaluate 11/12 match pairs with the only mismatch loci in A, B, C, or DR. However, given the expected rarity of such transplant pairs, we will include 7/8 MUD irrespective of DQ/DP matching status. The DQ/DP mismatch (and DP permissive vs. non-permissive, high expression/low expression) will be considered in a multivariate model to evaluate the independent impact of the MHC HopeSeq-derived risk score for acute GVHD.

Secondary endpoints:
For both Aims 1 and 2, we plan to evaluate the MHC PepSeq-predicted immunogenicity of the transplant pairs in other secondary clinical endpoints; chronic GVHD, 3-year overall survival, relapse-free survival, relapse, and non-relapse mortality.

Statistical considerations:
The goal of the proposed study is to establish the MHC PepSeq-based algorithm to predict aGVHD and cGVHD in alloHCT recipient of 8/8 and 7/8 MUD, separately. We will develop the algorithm in the following steps:

- Retrieve clinical information on patient-, disease-, and transplant-related characteristics, the primary endpoints (acute GVHD, chronic GHVD), and secondary endpoints (relapse, NRM, disease-free survival, and overall survival);
- Merge clinical information with the annotated MCH PepSeq data;
- Randomly assign 2/3 of subjects to a training set, and 1/3 of subjects to validation set;
- Use random survival forests for competing risks to identify present peptides that predict acute or chronic GVHD in the training set. Variable importance and minimal depth measures will be used for feature selection;
- Use multivariable Fine and Gray proportional hazards model of acute or chronic GVHD including both clinical factors and selected peptides in the training set;
- Assign weight for each peptide in the final multivariable model based on the adjusted HR. The reference group will be changed if the estimated HR< 1.
  Adjusted HR of 1.2 or less will be dropped from considerations
  Adjusted HR of 1.3 to 2.0 will be assigned a weight of 1,
  Adjusted HR of 2.1 to 3.0 will be assigned a weight of 2,
  Adjusted HR of 3.1 to 4.0 will be assigned a weight of 3.
  Adjusted HR of 4.1 to 5.0 will be assigned a weight of 4.
  Adjusted HR of 5.1 or more will be assigned a weight of 5.
- The MHC PepSeq score will be sum of these integer weights.
- Apply the same MHC PepSeq scoring in the validation set; and
- Evaluate the prediction performance of the MHC PepSeq score on acute or chronic GVHD in the validation set using the multivariable model including the same clinical factors as the final model in the training set. C-index and AUC will be used to evaluate the prediction performance.

Non-CIBMTR data source:
N/A

Conflicts of interest:
None

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Characteristics of patients receiving first allo-HCT from an unrelated donor for AML, ALL, MDS from 2000-2017, as reported to the CIBMTR

Characteristic	8/8 MUD	7/8 mMUD
No. of patients	6167	1716
No. of centers	219	186
Age at HCT		
Median (min-max)	52.62 (0.45-83.42)	45.54 (0.7-76.4)
<10	310 (5)	116 (6.8)
10-17	284 (4.6)	149 (8.7)
18-29	671 (10.9)	241 (14)
30-39	588 (9.5)	208 (12.1)
40-49	913 (14.8)	296 (17.2)
50-59	1500 (24.3)	388 (22.6)
60-69	1559 (25.3)	284 (16.6)
≥70	342 (5.5)	34 (2)
Gender		
Male	3567 (57.8)	937 (54.6)
Female	2600 (42.2)	779 (45.4)
Disease		
AML	2598 (42.1)	765 (44.6)
ALL	1016 (16.5)	381 (22.2)
MDS	2553 (41.4)	570 (33.2)
DP mismatch		
No	131 (2.1)	33 (1.9)
Yes	3660 (59.3)	1022 (59.6)
Missing	2376 (38.5)	661 (38.5)
Graft type		
Bone marrow	1603 (26)	532 (31)
Peripheral blood	4564 (74)	1184 (69)
GVHD prophylaxis		
CD34 selection	114 (1.8)	47 (2.7)
TAC + MMF ± other(s) (except post-CY)	997 (16.2)	265 (15.4)
TAC + MTX ± other(s) (except MMF, post-CY)	3198 (51.9)	780 (45.5)
TAC + other(s) (except MMF, MTX, post-CY)	346 (5.6)	89 (5.2)
TAC alone	151 (2.4)	51 (3)
CSA + MMF ± other(s) (except post-CY)	280 (4.5)	80 (4.7)
CSA + MTX ± other(s) (except MMF, post-CY)	878 (14.2)	314 (18.3)
CSA + other(s) (except MMF, MTX, post-CY)	45 (0.7)	24 (1.4)
CSA alone	53 (0.9)	28 (1.6)
Other(s)	58 (0.9)	19 (1.1)
Missing	47 (0.8)	19 (1.1)

Characteristic	8/8 MUD	7/8 mMUD
Conditioning regimen intensity		
MAC	4079 (66.1)	1247 (72.7)
RIC	2088 (33.9)	469 (27.3)
Acute GVHD		
No	3206 (52)	807 (47)
Yes	2961 (48)	909 (53)
Chronic GVHD		
No	3196 (51.8)	899 (52.4)
Yes	2971 (48.2)	817 (47.6)
Year of HCT		
2000	100 (1.6)	45 (2.6)
2001	124 (2)	64 (3.7)
2002	140 (2.3)	57 (3.3)
2003	202 (3.3)	111 (6.5)
2004	324 (5.3)	118 (6.9)
2005	433 (7)	149 (8.7)
2006	520 (8.4)	154 (9)
2007	590 (9.6)	188 (11)
2008	466 (7.6)	172 (10)
2009	488 (7.9)	145 (8.4)
2010	367 (6)	92 (5.4)
2011	266 (4.3)	46 (2.7)
2012	314 (5.1)	53 (3.1)
2013	497 (8.1)	93 (5.4)
2014	449 (7.3)	86 (5)
2015	391 (6.3)	70 (4.1)
2016	264 (4.3)	52 (3)
2017	232 (3.8)	21 (1.2)
Follow-up of survivors, months - median (min-max)	104.84 (3.19-219.84)	119.87 (1.61-216.58)

Proposal: 1911-102

Title:
Machine learning models and clinical decision support tool for acute and chronic graft versus host disease (GvHD) in patients with acute myeloid leukemia (AML) undergoing allogeneic hematopoietic cell transplant (HCT).

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Research hypothesis:
We hypothesize that the predictive information contained in the data routinely collected for patients with AML undergoing allogeneic HCT as part of the CIBMTR reporting can be used in a set of machine learning models to develop a clinical decision support tool which will provide patients with more precise information regarding their likelihood of developing GvHD along with the type and severity of GvHD.

Specific aims:
According to SEER data, approximately 21,000 new cases of AML will be diagnosed in 2019, and only 28.3% of those patients will survive 5 years. Even though the median age of diagnosis for AML is 68 years, 66% of patients are young enough to be transplant eligible [1]. More than 34,000 AML patients have received an allogeneic HCT from 2006-2016 and have data reported to CIBMTR. GvHD is a major cause of morbidity and mortality in patients undergoing allogeneic HCT [2]. This project will use patient data collected (i.e. patient demographics, disease characteristics) for AML patients undergoing allogeneic HCT reported to CIBMTR to build different machine learning predictive models which will help improve understanding of the factors that play a role in whether or not an allogeneic HCT patient will

- Develop any grade acute or chronic GvHD during the first-year post transplant,
- Develop extensive chronic GvHD after the first 100 days,
- Develop grade 2-4 acute GvHD during the first 100 days.

The three points above are motivated by the fact that, a better understanding of the factors that influence them can help inform a patient's decision regarding whether or not to undergo transplant. To this end, the project will additionally incorporate the predictive models into a prototype clinical decision support tool that will provide the clinician with risk scores for individual patients (using the predictive model to provide these scores). The goal of the support tool is to provide the physician and patient with predicted risk and expected outcome information based on their personal information—actionable information that can help patients understand their risks when choosing to undergo an allogeneic HCT.

<u>Specific aim 1:</u>
Build machine learning models to predict:

- The probability of a patient developing any grade acute and/or chronic GvHD during the first-year post-transplant;
- The probability of a patient developing extensive chronic GvHD after the first 100 days; and
- The probability of a patient developing grades 2-4 acute GvHD during the first 100 days.

<u>Specific aim 2:</u>
Incorporate the predictive models into a prototype clinical decision support tool that provides both physician and patient with pertinent and actionable information that supports their decision-making process.

Scientific impact:
Patients with AML undergoing allogeneic HCT have risks of developing acute and chronic GvHD, with an incidence ranging between 9-50% for grade II-IV acute GvHD and 15-56% for chronic GvHD [3]. Risk of dying from GvHD prior to day 100 is 8% and 11% for matched sibling donors and unrelated donors, respectively. After day 100 the risk of dying from GvHD is 10% for matched sibling donors and 12% for unrelated donors [2]. Generating machine learning predictive models and developing a clinical decision support tool would provide patients and their physicians with more precise information regarding the likelihood of developing GvHD along with the type and severity of GvHD. Knowledge gained from the predictive models may be used to inform patient care decisions. The clinical decision support tool would be tested for accuracy in predicting GvHD in prospective clinical trials. Choosing a different donor, selecting a different conditioning regimen, changing the prophylactic GvHD regimen, or modifying other risk factors for GvHD are just a few possibilities to minimize the risk of GvHD, if additional information was available to the clinician to predict the risk of developing GvHD.

Scientific justification:
There is a large amount of literature on factors associated with the development and severity of GvHD; however, there is a lot of conflicting information. In particular, a review by Harris et al. lists factors where one set of authors have found a positive association with GvHD for that factor while another set of authors have found no positive association with GvHD for the same factor. For example, Harris et al. found 3 papers indicating that "the risk for acute GvHD rises with increasing patient age", but also found that patient age was *not* "found to contribute to GvHD risk" [4]. Another issue with the literature is that a large portion of work focuses on the use of measures that are not generally available to clinicians when making decisions (i.e., the work uses test results and other data that is *not* part of the standard of care and not data routinely collected). Examples include the use of biomarkers ([5], [6]) and gene data ([7], [8], [9]). "Machine learning is the science of getting computers to learn and act like humans do, and improve their learning over time in autonomous fashion, by feeding them data and information in the form of observations and real-world interactions [10]." Hundreds and hundreds of data points are collected through CIBMTR reporting; however, only a fraction is being analyzed [2]. The group from Vanderbilt has used machine learning to evaluate chronic GvHD phenotypes and stratify survival in 339 patients who underwent allogeneic transplant for hematologic malignancies as part of chronic GvHD consortium study [11]. The work we propose is similar in nature to that of R. Shouval, et al. [12] who used a machine learning approach to predict overall mortality and produced an associated decision support tool, and even more similar to that of Lee, et al., [13] who used a machine learning approach to build models for risk prediction using "typically readily-available" clinical factors. The work in this study distinguishes itself from that of Lee, et al. by increasing the number of different questions being asked (from 2 very similar ones in Lee, et al. to 3 quite different ones in our case), as well as building an associated decision support tool that translates and presents the output from the models as coherent, clinically usable, and actionable information. The novelty of this study is that it will

- Simultaneously consider a wide variety of measures, so that any predictive information that results from the interaction between different measures will be captured,
- Use modeling techniques that capture non-linearity that is almost certainly present in the data, and
- Use measures which are available to anyone undergoing this transplant, so that the findings of this study can be easily implemented in a clinical setting via a decision support tool.

Patient eligibility population:

- Acute Myeloid Leukemia on comprehensive reporting tract
- Age $\geq$ 18 years old
- First allogeneic hematopoietic cell transplant

- Exclude ≥ 2 allogeneic transplants
- Years of transplant 2006 – 2016
- At least one year of follow up data reported to CIBMTR
- Patient consented to participate in CIBMTR database research study

Data requirements:

- Data Collection Forms: Pre-Transplant Essential Data, Recipient Baseline Data, Disease Classification, Post-Transplant Essential Data, Form 2010 AML Pre-Infusion Data, Form 2110 AML Post-Infusion Data, Post-HCT Follow Up Data (2100), Recipient Death Data, Six Month to Two Year Post HSCT Data (2200), Yearly Follow up for Greater than Two Years Post HSCT Data (2300)
- Supplemental data: None
- Combining CIBMTR data: No
- Variables Needed: Patient demographics: age, race, sex, performance status, comorbidities; Disease-related variables: AML classification, transformed from MDS, therapy related, predisposing syndrome, cytogenetics (Karyotype / FISH), molecular markers, CNS involvement; Induction chemotherapy (type, number of cycles); Disease status at transplant (induction failure, 1st CR, 2nd CR, ≥ 3rd CR, 1st relapse, 2nd relapse, ≥ 3rd relapse); Immunotherapy received (yes/no); Radiation therapy received (yes/no); Best disease status after transplant; Post-transplant therapy; Time from diagnosis to transplant; Median follow up; Acute GvHD (organ involvement, grade, stage); Chronic GvHD (organ involvement, grade, limited, extensive); GvHD treatments; Relapse date; Death date; Cause of death

Sample requirements:
None

Study design:
Observational study
Specific aim 1: Build machine learning models to predict

- The probability of a patient developing any grade acute and/or chronic GvHD during the first-year post-transplant;
- The probability of a patient developing extensive chronic GvHD after the first 100 days;
- The probability of a patient developing grades 2-4 acute GvHD during the first 100 days.

The first study aim involves building machine learning models that account for non-linear relationships in the data provided by CIBMTR. Building these models requires data that has been cleaned and formatted (the CIBMTR has already done most of the work in this regard with their forms and because the data is stored in a structured manner in a database). This specific aim would be addressed using the Pre-Transplant Essential Data and Baseline Recipient Data forms which collect patient demographics (age, sex, race, performance status) as well as comorbid conditions. Disease related information would be obtained from the Disease Classification form. Information about acute and chronic GvHD would be provided by the Post-HCT Follow-Up Data Form and the Post-Transplant Essential Data.

Specific aim 2:
Incorporate the predictive models into a prototype clinical decision support tool that provides both physician and patient with pertinent information that aids their decision-making process. The predictive models used in the prototypical clinical decision support tool will be derived from the data provided by CIBMTR (See Specific Aim 1).

Statistical methodology:
Descriptive statistics will be used to present patient, disease, and transplant variables. The data from CIBMTR will be divided into a training (75%) and testing (25%) datasets for specific aim 1. Statistics will be used to evaluate the prediction accuracy, precision, sensitivity, specificity and receiver operating characteristics (ROC) of the machine learning models. Kaplan-Meier survival and Cox proportional hazards models will be used to analyze overall survival as well as time from stem cell transplantation to development of acute and chronic GvHD.

Data sources:
CIBMTR Research Database

Conflicts of interest:
No conflicts of interest to report for either investigator.

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Characteristics of adult patients receiving first allo-HCT for AML between 2006-2016 with at least one year of follow-up data, as reported to the CIBMTR

Characteristic	N (%)
No. of patients	4332
No. of centers	215
Age at HCT	
Median (min-max)	51.02 (18.03-81.07)
18-29	586 (13.5)
30-39	577 (13.3)
40-49	898 (20.7)
50-59	1206 (27.8)
60-69	941 (21.7)
≥70	124 (2.9)
Gender	
Male	2306 (53.2)
Female	2026 (46.8)
Donor type	
HLA-identical sibling	1343 (31)
Other related	366 (8.4)
Well-matched unrelated (8/8)	1636 (37.8)
Partially-matched unrelated (7/8)	420 (9.7)
Mis-matched unrelated (≤ 6/8)	30 (0.7)
Multi-donor	9 (0.2)
Unrelated (matching TBD)	43 (1)
Cord blood	481 (11.1)
Missing	4 (0.1)
Graft type	
Bone marrow	603 (13.9)
Peripheral blood	3248 (75)
Cord blood	481 (11.1)
GVHD prophylaxis	
Ex-vivo T-cell depletion	75 (1.7)
CD34 selection	89 (2.1)
Post-CY + other(s)	275 (6.3)
Post-CY alone	3 (0.1)
TAC + MMF ± other(s) (except post-CY)	669 (15.4)
TAC + MTX ± other(s) (except MMF, post-CY)	1831 (42.3)
TAC + other(s) (except MMF, MTX, post-CY)	243 (5.6)
TAC alone	104 (2.4)
CSA + MMF ± other(s) (except post-CY)	430 (9.9)
CSA + MTX ± other(s) (except MMF, post-CY)	407 (9.4)

Characteristic	N (%)
CSA + other(s) (except MMF, MTX, post-CY)	32 (0.7)
CSA alone	46 (1.1)
Other(s)	37 (0.9)
Missing	91 (2.1)
Conditioning regimen intensity	
MAC	2714 (62.7)
RIC	1007 (23.2)
NMA	439 (10.1)
TBD	79 (1.8)
Missing	93 (2.1)
Year of HCT	
2006	540 (12.5)
2007	515 (11.9)
2008	569 (13.1)
2009	512 (11.8)
2010	428 (9.9)
2011	204 (4.7)
2012	200 (4.6)
2013	380 (8.8)
2014	362 (8.4)
2015	327 (7.5)
2016	295 (6.8)
Follow-up of survivors, months - median (min-max)	88.19 (12.01-149.93)

Proposal: 1911-270

Title:
Clinical Significance of Pediatric Late Acute GVHD and Chronic GVHD: Why Does It Matter to Differentiate?

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Research hypothesis:
We hypothesize that the development of either late acute graft-versus-host-disease (aGVHD) or chronic graft-versus-host-disease (cGVHD) has a significant negative impact on non-relapse mortality among children after allogeneic hematopoietic cell transplant (allo-HCT) but the clinical characteristics (e.g., incidence, organ involvement, treatment response, prognostic factors) of these two types of GVHD differ from each other.

Specific aims:
Aim 1:
To identify the incidence and risk factors of late aGVHD and cGVHD development among children with malignant and non-malignant disease

Aim 2:
To characterize the organ involvement in children with late aGVHD and cGVHD

Aim 3:
To assess the impact of late aGVHD and cGVHD on overall survival in children with late aGVHD and cGVHD following non-malignant diseases and NRM, relapse and overall survival in children with late aGVHD and cGVHD following malignant diseases

Scientific impact:
The present study will analyze the clinical presentation, risk factors, and outcomes of children with late aGVHD and cGVHD in children, and will help guide future research to develop better GVHD prophylaxis and treatment for pediatric late aGVHD and cGVHD.

Scientific justification:
Despite significant progress in the management of an early post-HCT complications including acute GVHD, late complications such as late aGVHD or cGVHD are less investigated, especially in children. Chronic GVHD remains a major cause of morbidity and mortality as well as long-term adverse quality of life in HSCT recipients[1,2]. Much less is known about late aGVHD; however, its clinical impact is likely be different from that of cGVHD because these two are considered biologically different[3].
Although the CIBMTR database has made a great contribution to the body of knowledge in pediatric GVHD, questions remain to be answered. First, no study using the CIBMTR database has specifically investigated late aGVHD in either adults or children. Only a few studies have focused on pediatric population. Jacobson et al. reported clinical course and prognostic factors of pediatric cGVHD; however, this data derived from 1995–2004 is not as applicable to the current era. Predictors of pediatric cGVHD development were reported by another more recent study from the data in 2000–2013, which mainly focused on the impact of age on HCT outcomes and did not investigate additional cGVHD factors[4]. Similarly, incidence of cGVHD among children in 2000–2014, without further analysis, was included in a

study as part of a composite outcome, GVHD-free relapse-free survival[5]. Moreover, all of these three studies excluded patients transplanted for nonmalignant diseases.
A recent multi-institutional study conducted by Pediatric Blood and Marrow Transplant Consortium reported the predictors of late aGVHD and cGVHD development and their detailed clinical manifestations in 243 children[7]. Incidence of late aGVHD and cGVHD were similar (24.3% and 21.0%, respectively). The use of peripheral blood graft and prior aGVHD were identified as independent predictors of both late aGVHD and cGVHD. Although the study thoroughly elucidated the presentation of cGVHD, it underrepresented some of pediatric subgroups such as non-malignancy and cord blood transplant (n = 21 and 22 for late aGVHD and/or cGVHD). Moreover, the study did not assess GVHD impact on non-relapse mortality, or prognostic factors in those children.
At the University of Minnesota, we recently conducted a retrospective review of 573 pediatric HCT from 2007 to 2017. The children with late aGVHD and/or cGVHD had a higher 2-year non-relapse mortality (Hazard Ratio: 2.8, 95%CI: 1.0–7.9, p=0.049) than those without. There was a trend towards better response to therapy in those with late aGVHD than with cGVHD (6-month CR/PR: 78% vs. 43%, respectively). However, because of the limited sample size, we could not perform many analytical statistics.

Patient eligibility population:
This proposed CIBMTR study will include all patients in the CIBMTR database, aged <18 years who had a first allo-HSCT in the year 2005–2017. We will exclude patients who had a donor lymphocyte infusion or second allo-HCT.

Data requirements:
The following variables will be collected from the CIBMTR database:

<u>Pre-treatment essential data (Form 2400 R5.0):</u>
Recipient data:
- Age
- sex

Donor information:
- Product type (bone marrow/PBSC/single umbilical cord unit/other product)
- donor type (related/unrelated)
- donor age
- donor sex
- CD34+ cell (total number)

*Other donor information: Ever pregnant (yes/no), blood type (A/B/AB/O), Rh (+/-), HLA match (matched or mismatched), CMV-antibodies (reactive/non-reactive)
Product processing/manipulation:
- T-cell depletion (yes/no)

Clinical Status of Recipient Prior to the conditioning:
- Functional status (Karnofsky/Lansky scale), Recipient CMV-antibodies (reactive/non-reactive)

Pre-HSCT preparative regimen:
- Conditioning regimen (myeloablative/non-myeloablative/reduced intensity conditioning), TBI (yes/no)

GVHD prophylaxis:
- (yes/no) to [ATG, corticosteroids, cyclosporine, cyclophosphamide, tacrolimus, methotrexate, mycophenolate, sirolimus, campath]

Disease classification (Form 2404 R3.0):

- Disease variables:
- Primary Disease for HCT (classified as "malignant" if ALL, AML, MDS, CML, and other malignancy vs. "non-malignant" if severe aplastic anemia, inherited erythrocyte abnormality, disorders of immune system, inherited disorders of metabolism, and other non-malignancies)

Post-HSCT Follow-up Data (Form 2100 R5.0):

aGVHD variables:

- aGVHD development:
    - aGVHD (yes/no), days to acute GVHD
- aGVHD grade/stage at diagnosis:
    - Overall grade, stage of skin (0-4), lower intestinal (0-4), upper intestinal (0-2), and liver (0-4)
- aGVHD grade/stage at maximum grade:
    - Timing (Posttransplant Day), overall grade, stage of skin (0-4), lower intestinal (0-4), upper intestinal (0-2), and liver (0-4)
- aGVHD therapy:
    - Topical only vs. steroids only vs. steroids + other agents

cGVHD variables:

- cGVHD development:
    - cGVHD (yes/no), days to cGVHD, onset (progressive/interrupted/de novo), functional status (Karnofsky/Lansky scale), platelets count, total serum bilirubin
- cGVHD grade/organ at diagnosis:
    - Overall grade (mild/moderate/severe/unknown, organ involvement
- cGVHD therapy: topical only vs steroids+ CNI vs steroids + others vs others

Sample requirements:

Biologic samples are not required for the present study.

Study design:

This is a retrospective cohort study aiming to describe the characteristics and investigate the clinical impact of late aGVHD and cGVHD in children who received an allo-HSCT in the year 2005-2017. This study will consist of two parts. The first part will examine the development and risk factors for late aGVHD and cGVHD in children in the database (i.e., late aGVHD or cGVHD among all pediatric HCT). The second part will focus on the patients who developed late aGVHD or cGVHD and explore the impact of GVHD specific factors them on subsequent outcomes

Non-CIBMTR data source:

External data source is not used in the present study.

Conflicts of interest:

None

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2. Jacobsohn DA, Arora M, Klein JP, et al. Risk factors associated with increased nonrelapse mortality and with poor overall survival in children with chronic graft-versus-host disease. *Blood.* 2011;118(16):4472-4479.
3. Holtan SG, Khera N, Levine JE, et al. Late acute graft-versus-host disease: a prospective analysis of clinical outcomes and circulating angiogenic factors. *Blood.* 2016;128(19):2350-2358.
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8. Inamoto Y, White J, Ito R, et al. Comparison of characteristics and outcomes of late acute and NIH chronic GVHD between Japanese and white patients. *Blood advances.* 2019;3(18):2764-2777.

Characteristics of patients age 0-21 receiving first allo-HCT from 2005-2017 and developed late aGVHD (>100 days post-HCT) or cGVHD, reported to the CIBMTR

Characteristic	Late aGVHD	cGVHD
No. of patients	194	2122
No. of centers	78	191
Age at HCT		
Median (min-max)	9 (0-21)	10 (0-21)
<10	104 (54)	1027 (48)
10-17	66 (34)	756 (36)
18-29	24 (12)	339 (16)
Gender		
Male	116 (60)	1267 (60)
Female	78 (40)	855 (40)
Disease		
AML	37 (19)	445 (21)
ALL	40 (21)	547 (26)
Other leukemia	1 (1)	13 (1)
CML	5 (3)	68 (3)
MDS	12 (6)	124 (6)
Other acute leukemia	1 (1)	54 (3)
NHL	0	48 (2)
HD	3 (2)	17 (1)
PCD/MM	0	1 (0)
Other malignancy	0	6 (0)
Non-malignant	93 (48)	794 (37)
Other	2 (1)	5 (0)
Donor type		
HLA-identical sibling	30 (15)	393 (19)
Other related	20 (10)	183 (9)
Well-matched unrelated (8/8)	39 (20)	482 (23)
Partially-matched unrelated (7/8)	16 (8)	203 (10)
Mis-matched unrelated (≤ 6/8)	3 (2)	35 (2)
Multi-donor	0	7 (0)
Unrelated (matching TBD)	1 (1)	18 (1)
Cord blood	85 (44)	799 (38)
Missing	0	2 (0)
GVHD prophylaxis		
Ex-vivo T-cell depletion	7 (4)	62 (3)
CD34 selection	2 (1)	35 (2)
Post-CY + other(s)	9 (5)	63 (3)
Post-CY alone	0	1 (0)

Characteristic	Late aGVHD	cGVHD
TAC + MMF ± other(s) (except post-CY)	32 (16)	214 (10)
TAC + MTX ± other(s) (except MMF, post-CY)	32 (16)	402 (19)
TAC + other(s) (except MMF, MTX, post-CY)	9 (5)	76 (4)
TAC alone	2 (1)	20 (1)
CSA + MMF ± other(s) (except post-CY)	39 (20)	437 (21)
CSA + MTX ± other(s) (except MMF, post-CY)	28 (14)	503 (24)
CSA + other(s) (except MMF, MTX, post-CY)	28 (14)	192 (9)
CSA alone	1 (1)	54 (3)
Other(s)	1 (1)	17 (1)
Missing	4 (2)	46 (2)
Conditioning regimen intensity		
MAC	134 (69)	1627 (77)
RIC	35 (18)	177 (8)
NMA	21 (11)	220 (10)
TBD	4 (2)	57 (3)
Missing	0	41 (2)
Year of HCT		
2005	16 (8)	297 (14)
2006	11 (6)	295 (14)
2007	19 (10)	283 (13)
2008	12 (6)	252 (12)
2009	29 (15)	244 (11)
2010	14 (7)	138 (7)
2011	12 (6)	79 (4)
2012	15 (8)	82 (4)
2013	15 (8)	119 (6)
2014	8 (4)	106 (5)
2015	19 (10)	92 (4)
2016	11 (6)	69 (3)
2017	13 (7)	66 (3)
Time to onset of aGVHD		
100 days - 4 months	66 (34)	-
4 - 6 months	77 (40)	-
6 - 12 months	44 (23)	-
> 12 months	7 (4)	-
Time to onset of cGVHD		
≤ 6 months	-	1136 (54)
6 - 12 months	-	650 (31)
> 1 year	-	219 (10)
Missing	-	117 (6)
Maximum grade of cGVHD		

Characteristic	Late aGVHD	cGVHD
Limited	-	847 (40)
Extensive	-	1255 (59)
Missing	-	20 (1)
Overall severity of cGVHD		
Mild	-	1113 (52)
Moderate	-	536 (25)
Severe	-	429 (20)
Missing	-	44 (2)
Follow-up of survivors, months - median (min-max)	70 (5-148)	91 (3-173)

Proposal: 1911-25

Title:
Influence of Combination of GVHD prophylaxis and stem cell source on GRFS

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Hypothesis:
PB stem cell source with in vivo T cell depletion or post transplant Cy is non inferior to bone marrow stem cell source Regarding GRFS in SCT for malignant hematological disorders

Specific aims:
- GRFS of Pts with malignant disorders treated with SCT stratified by stem cell source combined with gvhd prophy
- OS and PFS

Scientific justification:
Multiple studies were published looking at peripheral blood stem cells (PBSC) vs bone marrow as source of stem cell and showed better outcomes with BM as a source for stem cells but in these studies most of the pts with PB SC as a source were pts who had MAC regimens and did not get in vivo T cell Depletion. PB stem is still and important source of stem cells especially that it helps donors agree to volunteer and join the registry. In real practice the question of PBSc with in vivo T cell depletion with ATG , alemtuzumab or even post transplant Cy vs BM without in vivo T cell depletion is important to answer.

Patient eligibility population:
Patients with AML ALL MDS MPN lymphoid malignancies
age >=18
Matched related and Matched and mismatched unrelated donors
Year of HSCT >=2005
Bone marrow without in vivo T cell depletion group vs PB with in vivo T cell depletion ATG alemtuzumab or post SCT Cy
HSCT with myeloablative, reduced intensity regimen and non myeloablative regimens

Data requirements:
<u>This study will use the following forms:</u>
- Acute Myelogenous Leukemia, ALL and MDS/MPN and lymphoid malignancies Pre-HSCT Data
- Acute Myelogenous Leukemia, ALL and MDS/MPN and lymphoid malignancies Post-HSCT Data
- Pre-Transplant Essential Data
- Post-transplant Essential data

<u>List of variables needed:</u> Age of patient at diagnosis, gender of patient and donor , date of diagnosis, date of HSCT, Donor type, conditioning regimen, GVHD prophylaxis, date of death, date of last follow up.

Sample requirements:
None

Study design:
Data will be collected and analyzed. We will retrospectively reviewed patients who had-HSCT since year 2005 to treat Hematological malignancies and decided into 2 groups PB with invivo T cell depletion or post SCT Cy vs BM without In vivo T cell depletion or post Tx Cy
Objectives are to explore
Demographics, disease-related and transplant-related variables mentioned above will be collected. GRFS will be calculated as the time from transplantation until the earliest occurrence of any event: relapse, death, or GVHD. PFS is defined as the time from HSCT to the time of progression, death or last contact whichever occurred first. OS is defined as the time from HSCT to the time of death or last contact. OS and PFS will be estimated using the Kaplan-Meier method.

Non-CIBMTR data source:
none

References:
1. Amouzegar et al . Peripheral Blood or Bone Marrow Stem Cells? Practical Considerations in Hematopoietic Stem Cell Transplantation, transfusion Medicine review lume 33, Issue 1, January 2019, Pages 43-50

Characteristics of patients receiving first allo-HCT for hematologic malignancy with specified graft and GVHD prophylaxis combination from 2005-2019, as reported to the CIBMTR

Characteristic	ATG/Campath/PT-cy	BM, no PB, ATG/Campath/PT-cy
No. of patients	1951	5229
No. of centers	171	227
Age at HCT		
Median (min-max)	45.36 (18.01-76.24)	56.12 (18.01-83.42)
18-29	475 (24.3)	454 (8.7)
30-39	305 (15.6)	475 (9.1)
40-49	418 (21.4)	824 (15.8)
50-59	478 (24.5)	1512 (28.9)
60-69	234 (12)	1701 (32.5)
≥70	41 (2.1)	263 (5)
Gender		
Male	1065 (54.6)	3076 (58.8)
Female	885 (45.4)	2153 (41.2)
Missing	1 (0.1)	0
Disease		
AML	817 (41.9)	1996 (38.2)
ALL	330 (16.9)	405 (7.7)
Other leukemia	41 (2.1)	298 (5.7)
CML	205 (10.5)	210 (4)
MDS	359 (18.4)	1606 (30.7)
Other acute leukemia	27 (1.4)	33 (0.6)
NHL	134 (6.9)	501 (9.6)
HD	23 (1.2)	112 (2.1)
PCD/MM	15 (0.8)	68 (1.3)
Donor type		
HLA-identical sibling	619 (31.7)	1110 (21.2)
Well-matched unrelated (8/8)	1051 (53.9)	2983 (57)
Partially-matched unrelated (7/8)	252 (12.9)	997 (19.1)
Mis-matched unrelated (≤6/8)	29 (1.5)	139 (2.7)
GVHD prophylaxis		
Ex-vivo T-cell depletion	50 (2.6)	72 (1.4)
CD34 selection	5 (0.3)	140 (2.7)
Post-CY + other(s)	0	291 (5.6)
Post-CY alone	0	3 (0.1)
TAC + MMF ± other(s) (except post-CY)	165 (8.5)	969 (18.5)
TAC + MTX ± other(s) (except MMF, post-CY)	1025 (52.5)	1837 (35.1)
TAC + other(s) (except MMF, MTX, post-CY)	39 (2)	190 (3.6)

Characteristic	ATG/Campath/PT-cy	BM, no PB, ATG/Campath/PT-cy
TAC alone	21 (1.1)	222 (4.2)
CSA + MMF ± other(s) (except post-CY)	74 (3.8)	523 (10)
CSA + MTX ± other(s) (except MMF, post-CY)	482 (24.7)	491 (9.4)
CSA + other(s) (except MMF, MTX, post-CY)	5 (0.3)	155 (3)
CSA alone	30 (1.5)	169 (3.2)
Other(s)	19 (1)	89 (1.7)
Missing	36 (1.8)	78 (1.5)
Conditioning regimen intensity		
MAC	1596 (81.8)	2249 (43)
RIC	280 (14.4)	2312 (44.2)
NMA	45 (2.3)	530 (10.1)
TBD	25 (1.3)	111 (2.1)
Missing	5 (0.3)	27 (0.5)
Year of HCT		
2005	399 (20.5)	545 (10.4)
2006	342 (17.5)	542 (10.4)
2007	250 (12.8)	532 (10.2)
2008	158 (8.1)	557 (10.7)
2009	156 (8)	496 (9.5)
2010	96 (4.9)	236 (4.5)
2011	31 (1.6)	200 (3.8)
2012	58 (3)	231 (4.4)
2013	91 (4.7)	398 (7.6)
2014	106 (5.4)	411 (7.9)
2015	80 (4.1)	346 (6.6)
2016	63 (3.2)	284 (5.4)
2017	60 (3.1)	246 (4.7)
2018	53 (2.7)	174 (3.3)
2019	8 (0.4)	31 (0.6)
Follow-up of survivors, months - median (min-max)	95.49 (1.71-172.76)	79.44 (0.03-172.99)

Proposal: 1912-01

Title:
Exploring the impact of Allogeneic Stem Cell Transplant Volume on GRFS: a matched cohort study in contemporary era.

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Hypothesis:
We hypothesize that the outcomes of patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) proceeding to allogeneic stem cell transplant (alloSCT) in first complete remission at higher-volume centers will have favorable graft-versus-host disease *(*GVHD*)/*relapse-free survival (GRFS) compared to those treated at lower-volume centers.

Rationale:
As a post remission strategy, alloSCT is potentially curative in patients with MDS and AML (1). Adverse GVHD following alloSCT could hinder the success rate of transplant and is a major source of non-relapse mortality (NRM)(1). Relapse post-alloSCT can be seen in about 30- 60% of patients and is the commonest cause of treatment failure (2). Therefore, the measurement survival in the absence of significant GVHD, relapse or death is an ideal outcome measure to consented patients seeking alloSCT. GVHD-free relapse free survival (GRFS) is one such composite endpoint that is increasingly recognized as a reliable metric to measure post-alloSCT success (3, 4). GRFS is defined as survival in the absence of acute grade 3/4 GVHD, chronic GVHD (cGVHD) requiring systemic immunosuppression, or relapse (3, 4). Understanding the morbidity and mortality associated with cGVHD, cGVHD free relapse free survival is another endpoint that is increasingly gaining traction in the field.
Beyond patient-specific and disease-related factors, the short and long-term outcomes of patients with AML or MDS have been previously shown to be influenced by institution or center-related factors. A large (n>60,000), retrospective study of AML patients treated in the United States reported that, after adjusting for patient and treatment-related factors, those patients receiving therapy and care at non-academic centers had inferior four-week mortality (odds ratio [OR]=1.52, 95% confidence interval [CI]: 1.46-1.59; p<0.0001) and 5-year OS (15% vs. 25%; p<0.0001) when compared to those receiving care at large academic centers (5). Indeed, center volume has been specifically shown to directly influence the outcomes of these patients. AML patients treated at higher-volume centers (>75th percentile) had lower mortality compared with those treated at lower-volume centers (<75th percentile)(1.6% vs. 5.0%; OR=3.26, 95% CI: 1.98-5.38; p<0.001) in a prior propensity score-matched analysis (6). Further, a study evaluating only AML patients aged $\geq$65 years (a population in which greater comorbidity and less organ reserve for therapy or complication tolerance) similarly reported lower four-week mortality (OR-0.50, 95% CI: 0.48-0.67; p<0.001) and one-year OS (OR=0.86, 95% CI: 0.58-.78; p<0.001) for those treated at higher-volume centers compared to lower-volume centers for the overall cohort, with similar observations across subcategories including age groups and comorbidity status (7). Our group has also shown a favorable outcome including improved survival for patients with lymphoma receiving care at large volume centers (8).
Despite a growing intricate link between the volume of disease burden and the number of procedure performed at an organizational level that could influence clinical outcomes, its relevance as related to allo-SCT is unknown. We note with great interest that many practice changing scientific contributions in

the field of ASCT addressing relapse and NRM often emanate from large transplant volume centers with significant sub-specialty transplant expertise. Here we hypothesize that large volume centers may be more adept (resource, guideline adherence, expertise etc:) at early recognition and mitigating negative sequelae by proactive measures following ASCT. For a complication like GVHD it is important that timely interventions and appropriate sequencing of drugs is delivered by experts. To gain unprecedent insights on whether clinical volume may be a crucial factor influencing post-transplant outcomes our proposal has the following aims

- Examine within CIBMTR database to ascertain a link between the impact of the volume of alloSCT performed by centers on post-transplant GRFS for patients with MDS/AML undergoing transplant in CR1.
- Determine difference in GVHD prophylaxis strategy used at large vs low volume centers
- Determine clinical trial portfolio abundance for aGVHD, CGVHD, relapse reduction and infection mitigation between large volume transplant centers vs others.
- Evaluate cumulative incidence of grade ¾ aGVHD, cGVHD requiring systemic immunosuppression for the two cohorts (Events contributing to GRFS and CRFS)
- Differences in relapse vs non-relapse mortality between large volume and small volume transplant centers.
- Identify differences in rates of donor lymphocyte infusion used for treating post-transplant relapse and post-transplant maintenance studies to prevent relapses for the 2 groups
- Duration of hospital stay within first 100days for the 2 groups
- Factors associated with superior OS and leukemia free survival in the 2 groups
- immune-reconstitution D+30 and D+100

Scientific Justification: We anticipate the results from this study will help 1) Patients- choose transplant centers based on evidence. If our hypothesis is correct, likely clinical volume may be an important factor in high quality transplant care in modern era 2) Investigators and industry to cross-collaborate and increase access to trials at small volume centers (may also benefit expert investigators to seek further NIH funding in expanding GVHD/infection mitigation consortium work) 3) Facilitate policy makers to set up volume guidelines for human resource development and creating training programs 4) Integrate artificial intelligence in future to achieve all the above to help patients, investigators and policy makers.

Study inclusion:

- Patients aged 18-70 years with a diagnosis of AML or MDS proceeding to first alloSCT in CR1
- Receiving Peripheral Blood or Bone Marrow Grafts
- Human Leucocyte Antigen(HLA) matched (related or unrelated), 7/8 HLA mismatched
- T cell replete grafts

Exclusion:

- Patients without a diagnosis of AML or MDS.
- Age <18 years.
- alloSCT performed outside of frontline setting (e.g. for relapsed disease, CR2 or beyond, primary induction failure).

Data requirements:

CIBMTR report forms will be used for data analysis. Supplemental data if made available will also be used. Study period Jan 2011 to Dec 2017.

Pre-Transplant: Time from diagnosis to transplant, number of lines of induction/consolidation therapy used before alloSCT, HCTCI comorbidity index, disease status pre-transplant.
Transplant Center Information: Number of allo-transplants performed per year, type of center (academic vs non-academic, NCI designated cancer center vs others)
Donor: HLA matching level (matched vs mismatched- related/unrelated), Donor-recipient CMV/ABO matching status
Recipient: KPS, HCTCI, race, age, CMV, disease type/risk group
Graft: peripheral blood or bone marrow with no ex-vivo T cell depletion.
Therapy: Conditioning regimens (Intensity- MAC vs RIC, chemo or RT or chemo-RT), GVHD prophylaxis, maintenance post-alloSCT therapy to prevent relpase(Y/N), enrolled in a clinical trial for GVHD (Y/N, if yes number of clinical trials)
Disease related: Best response pre-transplant, time to relapse post-transplant. Rates of grade ¾ aGVHD, cGVHD and cGVHD requiring systemic steroids. Causes of death (relapse vs non-relapse).

Study design:
This will be a retrospective study reviewing post-alloSCT outcomes for adult patients (Age AML or MDS patients entering alloSCT in CR1.
Methods and Statistical Analysis: From the cumulative list we will distribute centers in to quartiles (25^{th}, 50^{th} and 75^{th}) to determine the total number of centers in each group. Subsequently they will be divided in to high volume (> 75% percentile) vs others (< 75^{th} percentile). Propensity matching to build a matched dataset controlling disease, donor, comorbidities, therapy, graft related metrics will be performed. If available NIH cGVHD criteria will be reported. CIBMTR aGVHD staging/grading criteria will be utilized for reporting. Relapse will be determined based on the time from HSCT till clinical recurrence of disease confirmed by morphology. Death without relapse will be treated as competing risk. Overall Survival is time from transplant till death from any cause and leukemia free survival is defined as time from ASCT to treatment failure (death or relapse).
Patient, disease and alloSCT-related factors will be compared between groups using the Chi-square test for categorical variables and the Wilcoxon two sample test for continuous variables. Kaplan-Meier product limit estimates will be used to calculate the probabilities of OS and PFS. Primary outcome of interest is the GRFS. The cumulative incidence of NRM and disease progression will be estimated accounting for competing risks for the two groups. MVA models will be built to determine risk factors for given outcome of interest at low and high volume centers. Descriptive stats will be offered to highlight the abundance of clinical trial portfolio for GVHD and relapse mitigation between the two cohorts.

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Characteristics of adult patients receiving first allo-HCT for AML in CR1 or MDS in CR from 2011-2017, reported to the CIBMTR

	Quartiles based on center allo-HCT volume			
Characteristic	**<=25%**	**26-50%**	**51-75%**	**>75%**
No. of patients	79	186	354	1095
No. of centers	40	39	38	38
Age at HCT				
Median (min-max)	54.51 (19.17-69.99)	56.42 (18.35-69.8)	57.06 (18.04-69.82)	57.36 (18.05-69.99)
18-29	11 (13.9)	13 (7)	32 (9)	82 (7.5)
30-39	6 (7.6)	21 (11.3)	37 (10.5)	86 (7.9)
40-49	11 (13.9)	26 (14)	41 (11.6)	153 (14)
50-59	24 (30.4)	62 (33.3)	108 (30.5)	333 (30.4)
60-69	27 (34.2)	64 (34.4)	136 (38.4)	441 (40.3)
Gender				
Male	49 (62)	106 (57)	194 (54.8)	604 (55.2)
Female	30 (38)	80 (43)	160 (45.2)	491 (44.8)
Disease				
AML	67 (84.8)	166 (89.2)	309 (87.3)	919 (83.9)
MDS	12 (15.2)	20 (10.8)	45 (12.7)	176 (16.1)
Donor type				
HLA-identical sibling	30 (38)	109 (58.6)	178 (50.3)	513 (46.8)
Well-matched unrelated (8/8)	36 (45.6)	67 (36)	151 (42.7)	502 (45.8)
Partially-matched unrelated (7/8)	13 (16.5)	10 (5.4)	25 (7.1)	80 (7.3)
Graft type				
Bone marrow	8 (10.1)	19 (10.2)	38 (10.7)	171 (15.6)
Peripheral blood	71 (89.9)	167 (89.8)	316 (89.3)	924 (84.4)
GVHD prophylaxis				
CD34 selection	0	0	5 (1.4)	34 (3.1)
Post-CY + other(s)	3 (3.8)	16 (8.6)	11 (3.1)	41 (3.7)
Post-CY alone	1 (1.3)	1 (0.5)	0	13 (1.2)
TAC + MMF ± other(s) (except post-CY)	14 (17.7)	18 (9.7)	63 (17.8)	118 (10.8)
TAC + MTX ± other(s) (except MMF, post-CY)	14 (17.7)	63 (33.9)	197 (55.6)	635 (58)
TAC + other(s) (except MMF, MTX, post-CY)	1 (1.3)	4 (2.2)	17 (4.8)	91 (8.3)
TAC alone	3 (3.8)	0	11 (3.1)	17 (1.6)
CSA + MMF ± other(s) (except post-CY)	10 (12.7)	16 (8.6)	6 (1.7)	57 (5.2)

	Quartiles based on center allo-HCT volume			
Characteristic	**<=25%**	**26-50%**	**51-75%**	**>75%**
CSA + MTX ± other(s) (except MMF, post-CY)	23 (29.1)	49 (26.3)	25 (7.1)	65 (5.9)
CSA + other(s) (except MMF, MTX, post-CY)	1 (1.3)	8 (4.3)	0	2 (0.2)
CSA alone	3 (3.8)	4 (2.2)	4 (1.1)	0
Other(s)	0	0	6 (1.7)	7 (0.6)
Missing	6 (7.6)	7 (3.8)	9 (2.5)	15 (1.4)
Conditioning regimen intensity				
MAC	38 (48.1)	83 (44.6)	192 (54.2)	603 (55.1)
RIC	27 (34.2)	79 (42.5)	144 (40.7)	400 (36.5)
NMA	5 (6.3)	12 (6.5)	13 (3.7)	55 (5)
TBD	2 (2.5)	4 (2.2)	3 (0.8)	21 (1.9)
Missing	7 (8.9)	8 (4.3)	2 (0.6)	16 (1.5)
Year of HCT				
2011	1 (1.3)	15 (8.1)	42 (11.9)	106 (9.7)
2012	9 (11.4)	8 (4.3)	37 (10.5)	118 (10.8)
2013	17 (21.5)	31 (16.7)	70 (19.8)	225 (20.5)
2014	13 (16.5)	35 (18.8)	55 (15.5)	237 (21.6)
2015	12 (15.2)	40 (21.5)	70 (19.8)	184 (16.8)
2016	13 (16.5)	32 (17.2)	50 (14.1)	125 (11.4)
2017	14 (17.7)	25 (13.4)	30 (8.5)	100 (9.1)
Follow-up of survivors, months - median (min-max)	34.28 (0.03-71.84)	35.82 (3.03-75.76)	49.05 (2.99-97.37)	60.26 (3.52-100.2)

Combined Proposal: 1906-03/1911-31/1911-139/1911-169/1911-196

Title:
Comparison of outcomes with post-transplant cyclophosphamide (pCY) in haploidentical donor transplant (HIDT) versus 8/8 HLA-matched related and unrelated, and 7/8 mismatched unrelated donor allogeneic stem cell transplantation for acute leukemia and myelodysplastic syndrome

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Research hypothesis:
Allogeneic hematopoietic stem cell transplantation (AHSCT) is a curative treatment for acute leukemia and myelodysplastic syndrome (MDS). However, only 25% of patients have availability of a matched related donor (MRD) and approximately 70% of patients can get a matched unrelated donor (MUD) (1). In such circumstances, haploidentical donor transplant (HIDT) has been used successfully and provides promising outcomes.
High dose post-transplant cyclophosphamide (pCY) is one of the commonly used GVHD prophylaxis in HIDT. It selectively depletes alloreactive proliferating T-cells, allowing for engraftment of hematopoietic stem cells despite HLA disparity. HIDT using pCY and bone marrow allograft is associated with a grade III-IV acute GVHD rate of 6% and one-year non-relapse mortality (NRM) rate of 15% (2), while a lower rate of extensive chronic GVHD is observed with one dose of pCY compared to two doses (5% vs 25%, p=0.05). HIDT with pCY has shown to provide equivalent long-term survival, relapse and NRM when compared to matched related and unrelated donor transplants using conventional GVHD prophylaxis (3-6).
Based on these promising results, the role of pCY as a single agent GVHD prophylaxis was assessed in HLA-matched related and unrelated bone marrow transplant and resulted in cumulative incidences of grade III to IV acute and chronic GVHD of 10% each (7). pCY in combination with cyclosporine in HLA-matched related and unrelated AHSCT using mobilized peripheral blood stem cells resulted in grade III-IV acute GVHD of 0% and extensive chronic GVHD rate of 30% (8). Recently, the EBMT reported outcomes of pCY as a single agent or in combination with one or two GVHD prophylaxis agents in 423 leukemia patients undergoing matched sibling and unrelated donor transplants and revealed that addition of two immunosuppressive agents to pCY was associated with reduced risk of extensive chronic GVHD (HR 0.25, p=0.02), NRM (HR 0.35, p=0.04), and improved overall survival (HR 0.49, p=0.02) (9).
Unfortunately, a comprehensive study evaluating outcome of pCY in HIDT versus 8/8 HLA-MRD and MUD, and 7/8 mismatched unrelated donor (MMUD) transplant is lacking. Additionally, data on comparative efficacy of pCY versus conventional GVHD prophylaxis regimens in HLA-MRD, MUD, and 7/8 MMUD are limited. Our hypothesis is that clinical outcomes using pCY are similar with haploidentical donors in comparison to matched related and matched unrelated donors. We believe that the CIBMTR database will provide us a large patient population to yield a strong evidence of efficacy of pCY (either as a single agent and in combination with other immunosuppressive agents).

Specific aims:
<u>Primary objective:</u>
Is to estimate GVHD-free relapse-free survival (GRFS) in HIDT, 8/8 MRD and MUD, and 7/8 MMUD AHSCT using pCY.

<u>Secondary objectives:</u>

- To evaluate cumulative incidence of acute and chronic GVHD in HIDT, 8/8 MRD and MUD, and 7/8 MMUD AHSCT using pCY.
- To evaluate relapse, overall survival (OS), relapse-free survival (RFS), and NRM in HIDT, 8/8 MRD and MUD, and 7/8 MMUD AHSCT using pCY.

Exploratory objective: A subgroups analysis evaluating outcomes between pCY and conventional GVHD prophylaxis in patients undergoing 8/8 HLA-MRD, MUD and 7/8 MMUD

Scientific impact:
If our hypothesis is correct and pCY does lead to similar outcomes after haploidentical donor transplants in comparison to matched or mismatched donor transplants, it will allow expansion of donor pool for thousands of patients who currently do not have a matched donor available. It will further reduce the delay associated with donor search and acquisition as almost all patients have a haploidentical donor available.

Scientific justification:
Approximately 40-50% of patients undergoing 8/8 HLA-MRD and MUD experience GVHD with conventional GVHD prophylaxis of a combination of calcineurin inhibitor and methotrexate or mycophenolate. Single center studies revealed the efficacy of pCY both as a single agent and in combination with another immunosuppressive agent in HLA-MRD and MUD AHSCT. The comparison of outcomes of pCY use among HIDT, 8/8 MRD and MUD, and 7/8 MMUD transplant may provide comparative efficacy in different settings.

Patient eligibility population:
- Pediatric and adult patients with acute leukemia (AML, ALL) and MDS who underwent their first AHSCT from the following donors: haploidentical donors, 8/8 HLA-MRD, 8/8 HLA-MUD or 7/8 HLA-MMUD between 2009 and 2018.A 7/8 MMUD is defined as single mismatch at either HLA-A, -B, -C or DRB1 loci.
- Patients with any disease status at transplant will be included
- Both bone marrow and peripheral blood stem cell allografts will be included
- Myeloablative conditioning, reduced intensity conditioning and nonmyeloablative regimens will be included

Data requirements:
We will collect following information:
<u>Patient specific:</u>
- Age
- Sex
- Race
- Ethnicity (Caucasian v African American v Hispanic v Other)
- KPS

<u>Disease specific:</u>
- Diagnosis
- Disease status at transplant

<u>Transplant specific</u>
- Conditioning regimen

- HLA match
- CMV serotyping
- ABO blood grouping
- GVHD prophylaxis
- CD34+ cell dose
- Engraftment

Outcomes:
- Neutrophil and platelet engraftment
- Graft failure
- Grade II-IV and III-IV acute GVHD
- Chronic GVHD
- Extensive chronic GVHD
- Incidence of CMV and EBV reactivation
- Overall survival (OS)
- Relapse rate
- Relapse-free survival (RFS)
- Non-relapse mortality (NRM)
- GVHD-free relapse-free survival (GRFS)

Sample requirements:
Since this is a retrospective review of available data, exact sample size is unknown at this time.
No biologic samples are needed.

Study design:
This will be a retrospective study involving patients with HIDT, HLA-MRD and MUD, and 7/8 MMUD AHSCT using the CIBMTR database. Study outcomes will be compared among these four groups using pCY. In addition, we plan to conduct a subgroup analysis comparing outcomes between pCY versus conventional GVHD prophylaxis in 8/8 HLA-MRD, MUD and 7/8 HLA-MMUD transplants.
Univariate and multivariate analysis will be used to ascertain factors responsible for the differences in outcomes. We will consider age (adult vs pediatric patients), conditioning regimen (myeloablative vs reduced intensity vs non-myeloablative), and source of stem cells (bone marrow vs peripheral blood) as variables to evaluate risk factors of GVHD as well as to assess the impact on these variables on long-term transplant outcomes.

Conflict of interest:
No

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Characteristics of patients receiving first allo-HCT for AML, ALL, or MDS between 2009-2018, as reported to the CIBMTR

Characteristic	8/8 MRD	Haploidentical	8/8 MUD	7/8 mMUD
No. of patients	4283	2090	4659	1031
No. of centers	217	177	202	155
Age at HCT				
Median (min-max)	55 (<1-78)	55 (1-88)	59 (<1-83)	55 (1-76)
<10	164 (4)	123 (6)	132 (3)	26 (3)
10-17	170 (4)	141 (7)	118 (3)	62 (6)
18-29	332 (8)	228 (11)	338 (7)	85 (8)
30-39	342 (8)	164 (8)	322 (7)	101 (10)
40-49	617 (14)	238 (11)	506 (11)	151 (15)
50-59	1192 (28)	409 (20)	1076 (23)	251 (24)
60-69	1284 (30)	608 (29)	1695 (36)	294 (29)
≥70	182 (4)	179 (9)	472 (10)	61 (6)
Gender				
Male	2488 (58)	1256 (60)	2752 (59)	570 (55)
Female	1795 (42)	834 (40)	1907 (41)	461 (45)
Disease				
AML	1884 (44)	1028 (49)	2071 (44)	500 (48)
ALL	690 (16)	433 (21)	479 (10)	135 (13)
MDS	1709 (40)	629 (30)	2109 (45)	396 (38)
Graft type				
Bone marrow	571 (13)	728 (35)	860 (18)	195 (19)
Peripheral blood	3712 (87)	1362 (65)	3799 (82)	836 (81)
GVHD prophylaxis				
PT-Cy based				
Post-CY + other(s)	133 (3)	1629 (78)	112 (2)	47 (5)
Post-CY alone	21 (<1)	3 (<1)	10 (<1)	1 (<1)
Non-PT-Cy based				
Ex-vivo T-cell depletion	16 (<1)	74 (4)	13 (<1)	8 (1)
CD34 selection	54 (1)	56 (3)	46 (1)	16 (2)
TAC + MMF ± other(s) (except post-CY)	501 (12)	126 (6)	831 (18)	172 (17)
TAC + MTX ± other(s) (except MMF, post-CY)	2060 (48)	68 (3)	2501 (54)	481 (47)
TAC + other(s) (except MMF, MTX, post-CY)	290 (7)	8 (<1)	300 (6)	77 (7)
TAC alone	80 (2)	13 (1)	97 (2)	26 (3)
CSA + MMF ± other(s) (except post-CY)	287 (7)	13 (1)	253 (5)	68 (7)
CSA + MTX ± other(s) (except MMF, post-CY)	609 (14)	30 (1)	266 (6)	83 (8)

Characteristic	8/8 MRD	Haploidentical	8/8 MUD	7/8 mMUD
CSA + other(s) (except MMF, MTX, post-CY)	20 (<1)	4 (<1)	19 (<1)	3 (<1)
CSA alone	52 (1)	4 (<1)	31 (1)	13 (1)
Other(s)	34 (1)	6 (<1)	49 (1)	10 (1)
Missing	126 (3)	56 (3)	131 (3)	26 (3)
Conditioning regimen intensity				
MAC	2605 (61)	972 (47)	2482 (53)	582 (56)
RIC	1333 (31)	343 (16)	1779 (38)	358 (35)
NMA	184 (4)	726 (35)	198 (4)	57 (6)
TBD	65 (2)	20 (1)	112 (2)	17 (2)
Missing	96 (2)	29 (1)	88 (2)	17 (2)
Year of HCT				
2009	513 (12)	59 (3)	686 (15)	223 (22)
2010	412 (10)	12 (1)	478 (10)	129 (13)
2011	250 (6)	15 (1)	348 (7)	64 (6)
2012	247 (6)	34 (2)	392 (8)	73 (7)
2013	465 (11)	154 (7)	683 (15)	143 (14)
2014	614 (14)	222 (11)	618 (13)	125 (12)
2015	535 (12)	313 (15)	530 (11)	119 (12)
2016	514 (12)	398 (19)	390 (8)	75 (7)
2017	396 (9)	444 (21)	319 (7)	44 (4)
2018	337 (8)	439 (21)	215 (5)	36 (3)
Follow-up of survivors, months - median (min-max)	49 (<1-125)	24 (1-126)	73 (3-128)	78 (<1-129)